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(54) Title: A SOLID DOSAGE FORM COMPRISING A FIBRATE AND A STATIN

(57) Abstract: The present invention relates to pharmaceutical compositions in particulate form or in solid dosage forms comprising a combination of a fibrate, notably fenofibrate, and a statin (also known as a HMG CoA reductase inhibitors), which compositions are manufactured without any need of addition of water or an aqueous medium and wherein at least 80% of the active substances (i.e. the fibrate and the statin) are present in the composition in dissolved form in order to ensure suitable bioavailability of both active ingredients upon oral administration.



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## A SOLID DOSAGE FORM COMPRISING A FIBRATE AND A STATIN

### Field of the invention

- The present invention relates to pharmaceutical compositions in particulate form or in solid dosage forms comprising a combination of a fibrate, notably fenofibrate, and a statin (also known as a HMG CoA reductase inhibitor). The compositions are manufactured without any need of addition of water or an aqueous medium. As a result, compositions having a very low content of moisture (less than 2% w/w water) are obtained, thereby ensuring suitable storage stability (both fibrates and statins are degradable by water).
- Furthermore, at least 80% of the active substances (i.e. the fibrate and the statin) are present in the composition in dissolved form, which ensures suitable bioavailability of both active ingredients upon oral administration.

### Background of the invention

- Fibrates are drug substances that generally are poorly and variably absorbed after oral administration. Normally they are prescribed to be taken with food in order to increase the bioavailability. There has been a number of improvements in dosage form of the currently most used fibrate, fenofibrate, in an effort to increase the bioavailability of the drug and hence its efficacy. Furthermore, clinical guidelines indicate that not only fibrate therapy but also a combination therapy with e.g. fenofibrate and a statin should be the most effective means of cholesterol and lipid management. In fact, treatment with fenofibrate is often prescribed together with treatment with a statin as clinicians seem to prefer the use of e.g. fenofibrate due to its triglyceride-lowering effects while a statin is used for its positive effects on lowering LDL-C and raising HDL-C. However, at present such a combination therapy can only be achieved by the use of two separate products, i.e. the patient needs to take e.g. one fenofibrate tablet together with another tablet or capsule containing a statin.

- As mentioned above, there has been an interest in obtaining improved compositions of fenofibrate and, accordingly, a number of publications relating to such compositions have emerged recently (see e.g. WO 04/041250). Although such compositions may lead to an improved fibrate therapy they do not meet the need for providing a composition containing a combination of a fibrate and a statin that is stable with respect to storage stability and at the same time leads to a suitable bioavailability of both active substances.

- WO 03/013608 describes compositions containing a fibrate and a statin. However, due to the manufacturing process (the active substances are melted together, filled into gelatin

capsules and allowed to cool) only capsules can be prepared. Furthermore, from a pharmaceutical point of view the manufacturing process seems to be difficult to up-scale taken into consideration the regulatory requirements with respect to e.g. mass variation, variation in drug content etc. Although the composition may appear as a solid

- 5 composition, there seems to be no flexibility in the formulation principle to provide other types of dosage forms than capsules.

Accordingly, there is a need for developing a pharmaceutical composition that in a single formulation contains a fibrate and a statin as active substances, which composition is

10 stable and provides suitable biopharmaceutical properties to the active substances (e.g. suitable bioavailability, less dependency on food intake etc), and which composition easily can be manufactured in large scale. Furthermore, there is a need for developing formulations containing a fibrate and a statin, which formulations can be further processed into pharmaceutical dosage forms with a high degree of flexibility of choosing the

15 particular kind of dosage form. Within the pharmaceutical field such a flexibility can be obtained when the formulation is in the form of a solid product in powder or particulate form. Accordingly, the present invention provides such a particulate material that is suitable for further processing into e.g. tablets.

- 20 In addition, there is still a need for a composition that has a suitable bioavailability, that can substantially reduce or overcome the differential between the bioavailability of the drug in patients who are fasted versus the bioavailability of the drug (in particular relevant for fenofibrate) in patients who are fed, and/or than can substantially reduce or overcome the intra- and/or inter-individual variations observed with the current treatment.
- 25 Furthermore, there is also a need for a composition that enables reduction in observed side effects.

- In general, it is known that the absorption and bioavailability of a therapeutically active substance can be affected by a variety of factors when administered orally. Such factors
- 30 include the presence of food in the gastrointestinal tract and, in general, the gastric residence time of a drug substance is significantly longer in the presence of food than in the fasted state. If the bioavailability of a drug substance is affected beyond a certain point due to the presence of food in the gastrointestinal tract, the drug substance is said to exhibit a food effect. Food effects are important because there is a risk associated with
- 35 administering the drug substance to a patient who has eaten recently. The risk derives from the potential that absorption into the bloodstream may be adversely affected to the point that the patient risks insufficient absorption to remedy the condition for which the

drug was administered. In the case of e.g. fenofibrate the situation is different in that food increases the uptake. Thus, lack of intake of food simultaneously with the drug substances may lead to insufficient absorption. The extent of absorption of a commercially available product Tricor® containing fenofibrate (from Abbott) is increased by  
5 approximately 35% under fed as compared to fasting conditions.

As described above, there remains a need for new pharmaceutical compositions comprising one or more fibrates exhibiting, suitable bioavailability of the active compound and/or reduced or eliminated food effect. In the present context, the term "suitable  
10 bioavailability" is intended to mean that administration of a composition according to the invention will result in a bioavailability that is improved compared to the bioavailability obtained after administration of the active substance(s) in a plain tablet; or the bioavailability is at least the same or improved compared to the bioavailability obtained after administration of a commercially available product containing the same active  
15 substance(s) in the same amounts. In particular it is desired to obtain quicker and larger and/or more complete uptake of the active compound, and thereby provide for a reduction of the administered dosages or for a reduction in the number of daily administrations. Further, pharmaceutical compositions of the invention may also reduce or negate the need for food to be taken simultaneously with the dosage form (in particular relevant for  
20 one or the active substances contained in a composition of the invention, namely the fibrate such as fenofibrate) thereby allowing patients more freedom on when the drug is taken.

### **Description of the invention**

25 The present invention provides pharmaceutical compositions in the form of particulate material and solid dosage forms for treatment of conditions that respond to fibrate and statin treatment.

As mentioned above, there is a need for developing pharmaceutical compositions  
30 containing a combination of a fibrate and a statin or a pharmaceutically acceptable salt thereof for oral use that lead to an improved treatment of conditions requiring lipid management (e.g. atherosclerosis, coronary heart diseases, diabetes management, obesity, overweight, metabolic syndrome etc.)

35 Furthermore, it would be beneficial to obtain an improved bioavailability, especially of the fibrate component, but as described below in some cases also for the statin component. A fibrate like fenofibrate has a very poor solubility in water, which property is regarded as

one of the major reasons for the poor bioavailability of fenofibrate. Accordingly, it would be an advantage to provide a composition in which the fibrate is mainly in dissolved form. The same applies to the statins that have poor water-solubility.

- 5 An improved bioavailability will lead to an improved treatment. It may also be possible to obtain the same therapeutic response with a decreased dose and/or a less frequent administration and less variability in plasma levels and no food restrictions. Another way of obtaining an improved treatment of conditions where e.g. fenofibrate is indicated is by balancing the release of fenofibrate to the gastro-intestinal tract in such a manner that an enhanced plasma concentration of fenofibrate is obtained initially or delayed with respect to the time of administration. A further therapeutic improvement would be to develop modified or delayed release compositions containing one or more fibrates.

- Especially, there is a need for developing a solid composition in particulate form that can be further processed into solid dosage form (e.g. tablets etc.). Such a composition must contain the active drug substances, i.e. the fibrate and the statin, mainly in dissolved form, but at the same time the composition must be in particulate form that can be further processed into a solid dosage form like e.g. tablets, i.e. the particulate material containing the active substances mainly in dissolved form must have suitable properties such as, e.g., suitable properties with respect to flowability, adherence (should be avoided), compressibility etc.

- In one aspect, the present invention relates to a particulate material comprising as active substances one or more fibrates and one or more statins, wherein at least 80% w/w of the total amount of active substances is dissolved in vehicle selected from the group consisting of a hydrophobic, a hydrophilic and a water-miscible vehicle.

- Normally, at least 85% w/w, at least 90% w/w, at least 95% w/w or at least 98% w/w of the total amount of active substances is dissolved in the vehicle.

- If those embodiments where 100% of the active substances are dissolved in the vehicle, the active substances are present in the form of a solid solution in the particulate composition. The presence of a solid solution can be tested by a DSC test mentioned herein. However, some crystallization of the active substances from solid solutions may be expected during storage. Accordingly, the present invention includes particulate material wherein the active substances are present in the form of a solid solution, but it is within the scope of the present invention that the active substances may precipitate upon

storage.

As mentioned above, sufficient flowability is required of the particulate material according to the invention in order to obtain a suitable flexibility so that different dosage forms can  
5 be obtained. Accordingly, a particulate material according to the invention has a suitable flowability as determined according to the method described in Ph.Eur. measuring the flow rate of the composition out of a funnel with a nozzle diameter of 10.0 mm.

A particulate material according to the invention comprises two active substances, namely  
10 a fibrate and a statin or a pharmaceutically acceptable salt thereof. In the following is given a description of the active substances.

#### *Fibrates*

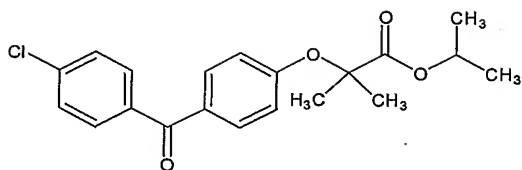
Fibrates includes gemfibrozil, fenofibrate, benzaifibrate, clofibrate and ciprofibrate. They  
15 are used as lipid regulating agents. They are regarded as prodrugs and are metabolized *in vivo* to their active metabolites.

In a specific embodiment the fibrate is fenofibrate or an analogue thereof. Normally, the concentration of fibrate in the vehicle is at least 10% w/w, based on the total weight of the  
20 fibrate, the statin and the vehicle. In particular, the concentration of fibrate in the vehicle is at least 15% w/w, or at least 16% w/w, or at least 17% w/w, or at least 20% w/w, preferably at least 25% w/w, more preferably at least 30% w/w, especially at least 35% w/w, based on the total weight of the fibrate, the statin and the vehicle.

25 For illustrative purposes only, the following is based on a specific example of a fibrate, namely fenofibrate. Thus, e.g. fenofibrate is metabolized to fenofibric acid that is the active substance. Fenofibric acid has an elimination half-life of about 20 hours. Measurement of the detected amount of fenofibric acid in the blood of a patient can reflect the efficacy of fenofibrate uptake.

30

Fenofibrate is chemically named 2-[4-(4-chlorobenzoyl)]-2-methyl-propanoic acid, 1-methylethyl ester and has the following structural formula:



Fenofibrate is a white solid that is insoluble in water. The melting point is 79-82°C.

5 Clinical studies have demonstrated that elevated levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C), and apolipoprotein B (apo B) are associated with human atherosclerosis. Decreased levels of high-density lipoprotein cholesterol (HDL-C) and its transport complex, apolipoprotein A (apo AI and apo AII) are associated with the development of atherosclerosis.

10 Fenofibrate is also effective in the treatment of diabetes type II.

Fenofibric acid, i.e. the active metabolite of fenofibrate, produces reductions in total cholesterol, LDL-cholesterol, apolipoprotein B, total triglycerides and triglyceride rich lipoprotein in treated patients. Furthermore, treatment with fenofibrate results in increases  
15 in HDL-cholesterol and apo AI and apo AII. Fenofibrate acts as a potent lipid regulating agent offering unique and clinical advantages over existing products in the fibrate family of drug substances. Fenofibrate produces substantial reduction in plasma triglyceride levels in hypertriglyceridemic patients and in plasma cholesterol and LDL-C in hypercholesterolemic and mixed dyslipidemic patients.

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Fenofibrate also reduces serum uric acid levels in hyperuricemic and normal subjects by increasing the urinary excretion of uric acid.

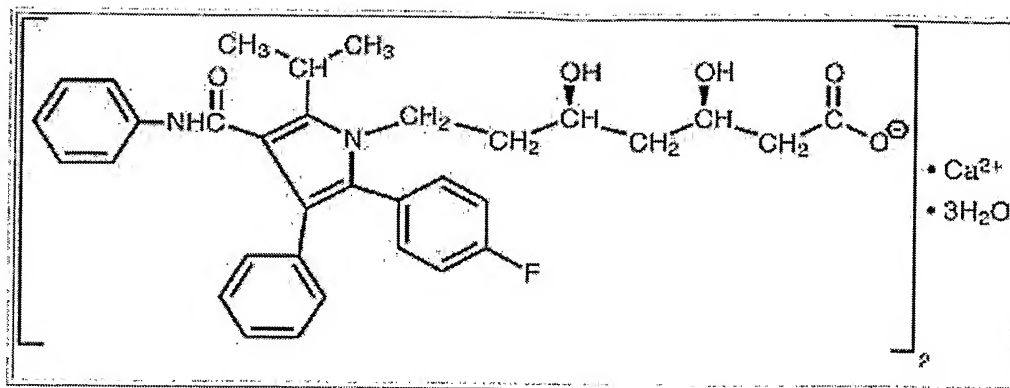
25 Fenofibrate is also indicated as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia). Improving glycemic control in diabetic patients showing fasting chylomicronemia will usually reduce fasting triglycerides and eliminate chylomicronemia and thereby obviating the need for pharmacological intervention.

30 *Statins*

- Statins include simvastatin, atorvastatin, lovastatin, pravastatin, rosuvastatin, pitavastatin and fluvastatin, and pharmaceutically acceptable salts thereof such as alkali metal and alkaline earth metal salts. Statins have a positive effect in the management of lipids and are used in the treatment of various diseases where it is of importance to control the lipid level in the plasma. In general the statins are well-absorbed (e.g. fluvastatin and simvastatin) after oral administration, although some of the statins have poor bioavailability (lovastatin has a bioavailability of about 30-40%, pravastatin about 30%, simvastatin about 5% and rosuvastatin about 50%). Some of the statins are water-soluble (e.g. pravastatin and fluvastatin) while other statins have a poor water-solubility (e.g. atorvastatin, lovastatin, pitavastatin, rosuvastatin and simvastatin). In general, the statins are sensible towards moisture, i.e. compositions without or with only a very little content of water are envisaged to have improved stability and the same applies for compositions that have been manufactured without use of an aqueous medium.
- The concentration of statin in the vehicle if a particulate material or solid dosage form according to the invention is at least 1% w/w, based on the total weight of the fibrate, the statin and the vehicle. More specifically, the concentration of statin in the vehicle is at least 1.5% w/w, or at least 2.5% w/w, or at least 5% w/w, or at least 7.5% w/w or at least 10% w/w, based on the total weight of the fibrate, the statin and the vehicle.
- In specific embodiment, the invention relates to a particulate material containing fenofibrate and simvastatin or a pharmaceutically acceptable salt thereof, a particulate material containing fenofibrate and atorvastatin or a pharmaceutically acceptable salt thereof, a particulate material containing fenofibrate and lovastatin or a pharmaceutically acceptable salt thereof, a particulate material containing fenofibrate and pravastatin or a pharmaceutically acceptable salt thereof, a particulate material containing fenofibrate and rosuvastatin or a pharmaceutically acceptable salt thereof, a particulate material containing fenofibrate and simvastatin or a pharmaceutically acceptable salt thereof.
- In the following is given examples on specific statins, however, the invention is not limited to these specific examples.

#### *Atorvastatin*





Atorvastatin calcium is a white to off-white crystalline powder that is insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile, slightly soluble in ethanol, and freely soluble in methanol.

Lipitor tablets for oral administration contain 10, 20, 40 or 80 mg atorvastatin and the following inactive ingredients: calcium carbonate, USP; candelilla wax, FCC; croscarmellose sodium, NF; hydroxypropyl cellulose, NF; lactose monohydrate, NF; magnesium stearate, NF; microcrystalline cellulose, NF; Opadry White YS-1-7040 (hydroxypropyl-methylcellulose, polyethylene glycol, talc, titanium dioxide); polysorbate 80, NF; simethicone emulsion.

Atorvastatin is a synthetic lipid-lowering agent. Atorvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis.

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Cholesterol and triglycerides circulate in the bloodstream as part of lipoprotein complexes. With ultracentrifugation, these complexes separate into HDL (high-density lipoprotein), IDL (intermediate-density lipoprotein), LDL (low-density lipoprotein), and VLDL (very-low-density lipoprotein) fractions. Triglycerides (TG) and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. LDL is formed from VLDL and is catabolized primarily through the high-affinity LDL receptor. Clinical and pathologic studies show that elevated plasma levels of total cholesterol (total-C), LDL-cholesterol (LDL-C), and apolipoprotein B (apo B) promote human atherosclerosis and are risk factors for developing cardiovascular

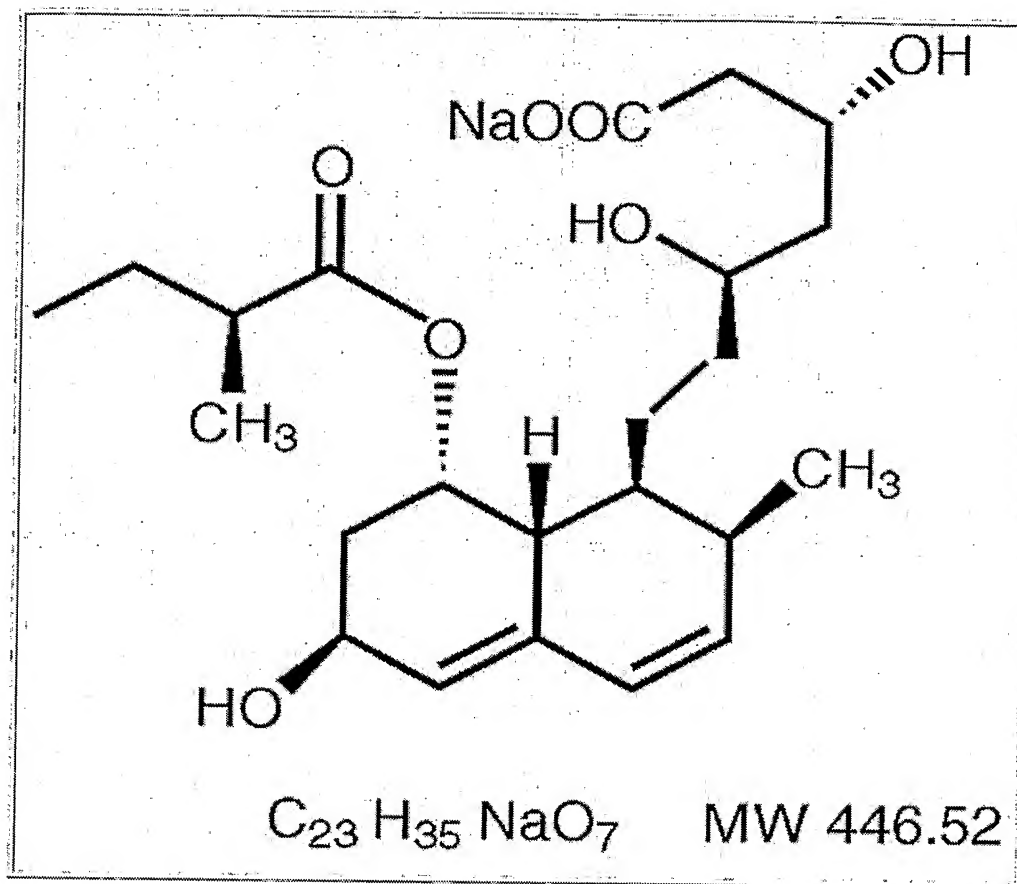
disease, while increased levels of HDL-C are associated with a decreased cardiovascular risk.

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. The absolute bioavailability of atorvastatin (parent drug) is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by C<sub>max</sub> and AUC, LDL-C reduction is said to be similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30% for C<sub>max</sub> and AUC) following evening drug administration compared with morning. However, LDL-C reduction is said to be the same regardless of the time of day of drug administration

#### *Pravastatin*

Pravastatin sodium (PRAVACHOL<sup>®</sup>) is one of a new class of lipid-lowering compounds, the HMG-CoA reductase inhibitors, which reduce cholesterol biosynthesis. These agents are competitive inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme catalyzing the early rate-limiting step in cholesterol biosynthesis, conversion of HMG-CoA to mevalonate.

Pravastatin sodium is designated chemically as 1-naphthalene-heptanoic acid, 1,2,6,7,8,8a-hexahydro-(beta),(beta),6-trihydroxy-2-methyl-8-(2-methyl-1-oxobutoxy)-, monosodium salt, [1S-[1(alpha)((beta)S\*,(beta)S\*),2(alpha),6(alpha),8(beta)(R\*),8a(alpha)]]-. The structural formula is shown below.



Pravastatin sodium is an odorless, white to off-white, fine or crystalline powder. It is a relatively polar hydrophilic compound with a partition coefficient (octanol/water) of 0.59 at a pH of 7.0. It is soluble in methanol and water (>300 mg/mL), slightly soluble in  
5 isopropanol, and practically insoluble in acetone, acetonitrile, chloroform, and ether.

PRAVACHOL is available for oral administration as 10 mg, 20 mg, 40 mg and 80 mg tablets. Inactive ingredients include: croscarmellose sodium, lactose, magnesium oxide, magnesium stearate, microcrystalline cellulose, and povidone. The 10 mg tablet also  
10 contains Red Ferric Oxide, the 20 mg and 80 mg tablets also contain Yellow Ferric Oxide, and the 40 mg tablet also contains Green Lake Blend (mixture of D&C Yellow No. 10-Aluminum Lake and FD&C Blue No. 1-Aluminum Lake).

Pravastatin produces its lipid-lowering effect in two ways. First, as a consequence of its  
15 reversible inhibition of HMG-CoA reductase activity, it effects modest reductions in intracellular pools of cholesterol. This results in an increase in the number of LDL-receptors on cell surfaces and enhanced receptor-mediated catabolism and clearance of circulating LDL. Second, pravastatin inhibits LDL production by inhibiting hepatic synthesis of VLDL, the LDL precursor.

Clinical and pathologic studies have shown that elevated levels of total cholesterol (Total-C), low density lipoprotein cholesterol (LDL-C), and apolipoprotein B (Apo B - a membrane transport complex for LDL) promote human atherosclerosis. Similarly, decreased levels of HDL-cholesterol (HDL-C) and its transport complex, apolipoprotein A, are associated with the development of atherosclerosis. Epidemiological investigations have established that cardiovascular morbidity and mortality vary directly with the level of Total-C and LDL-C and inversely with the level of HDL-C. Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, IDL, and remnants, can also promote atherosclerosis. Elevated plasma TG are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease. As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined. In both normal volunteers and patients with hypercholesterolemia, treatment with PRAVACHOL (pravastatin sodium) reduced Total-C, LDL-C, and apolipoprotein B. PRAVACHOL also reduced VLDL-C and TG and produced increases in HDL-C and apolipoprotein A. The effects of pravastatin on Lp (a), fibrinogen, and certain other independent biochemical risk markers for coronary heart disease are unknown. Although pravastatin is relatively more hydrophilic than other HMG-CoA reductase inhibitors, the effect of relative hydrophilicity, if any, on either efficacy or safety has not been established.

Pravastatin, like other HMG-CoA reductase inhibitors, has variable bioavailability. The coefficient of variation (CV), based on between-subject variability, was 50% to 60% for AUC. Pravastatin 20 mg was administered under fasting conditions in adults. The geometric means of  $C_{max}$  and AUC ranged from 23.3 to 26.3 ng/mL and from 54.7 to 62.2 ng\*hr/mL, respectively.

#### *Rosuvastatin*

Rosuvastatin is a potent HMG-CoA reductase inhibitor (statin). Rosuvastatin has been approved for treatment of primary hypercholesterolemia, mixed dyslipidemia, hypertriglyceridemia, and homozygous familial hypercholesterolemia. It has produced greater reductions in low-density lipoprotein (LDL)-cholesterol than atorvastatin, simvastatin, and pravastatin

35

Dose range is 5 to 40 milligrams (mg) orally once daily, with starting doses of 5 to 20 mg once daily. Doses may be titrated to 40 mg/day in those who do not meet their lipid

lowering goals on 20 mg/day. The drug may be given with or without food at any time of day. Dose adjustments are suggested for patients with severe renal impairment and those receiving concomitant cyclosporine or gemfibrozil.

- 5 Peak plasma levels have occurred 3 to 5 hours after oral doses, and were linear over the dose range of 5 to 80 mg; accumulation at steady-state is minimal. Rosuvastatin appears to be taken up selectively by hepatic versus nonhepatic tissue, attributed to relative hydrophilicity. The drug undergoes only minimal hepatic metabolism, and most of a dose is excreted via bile. The bioavailability is approximately 20%.

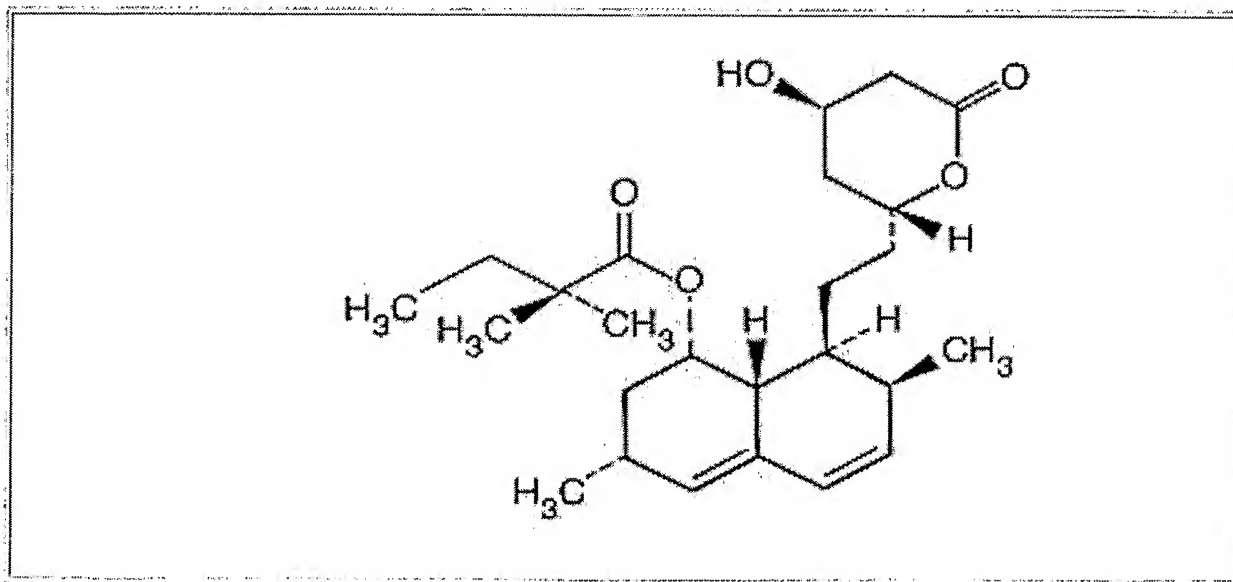
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### *Simvastatin*

Simvastatin is a lipid-lowering agent that is derived synthetically from a fermentation product of *Aspergillus terreus*. After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed to the corresponding (beta)-hydroxyacid form. This is an inhibitor of

15 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol.

- Simvastatin is butanoic acid, 2,2-dimethyl-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)-ethyl]-1-naphthalenyl ester, [1S-[1(alpha),3(alpha),7(beta),8(beta)(2S\*,4S\*),-8a(beta)]]]. The empirical formula of simvastatin is  $C_{25}H_{38}O_5$  and its molecular weight is 418.57. Its structural formula is:
- 20



Simvastatin is a white to off-white, nonhygroscopic, crystalline powder that is practically insoluble in water, and freely soluble in chloroform, methanol and ethanol.

Tablets ZOCOR® for oral administration contain either 5 mg, 10 mg, 20 mg, 40 mg or 80 mg of simvastatin and the following inactive ingredients: cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxides, lactose, magnesium stearate, starch, talc, titanium dioxide and other ingredients. Butylated hydroxyanisole is added as a  
5 preservative.

Elevated plasma levels of total cholesterol (total-C), LDL-C, and apolipoprotein B (Apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease, while increased levels of high-density lipoprotein cholesterol (HDL-C) and its  
10 transport complex, Apo A-I, are associated with decreased cardiovascular risk. High plasma triglycerides (TG) and cholesterol-enriched TG-rich lipoproteins, including very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), and remnants, can also promote atherosclerosis. Elevated plasma TG is frequently found in a triad with low HDL-C and small LDL particles, as well as in association with non-lipid metabolic risk  
15 factors for CHD. As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL-C or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined. Simvastatin has been shown to reduce both normal and elevated LDL-C concentrations. LDL is formed from very-low-density lipoprotein (VLDL) and is  
20 catabolized predominantly by the high-affinity LDL receptor.

Simvastatin undergoes extensive first-pass extraction in the liver, its primary site of action, with subsequent excretion of drug equivalents in the bile. As a consequence of extensive hepatic extraction of simvastatin (estimated to be > 60% in man), the availability of drug to  
25 the general circulation is low.

The present invention provides particulate material and solid dosage forms for improved treatment of conditions that respond to fibrate and statin treatment. Furthermore, such compositions and solid dosage form may also include or be used in combination with e.g.  
30 other active substances such as, e.g., other antilipidemic agents or antidiabetic type II substances like e.g. glimepiride, glibenclamide, gliclazid, repaglinid, nateglinid, metformine, pioglitazon, rosiglitazin, or acarbose. Also combinations with cholesterol absorption inhibitors like ezetimibe and cholesterol scavengers like colessevelam. They may also be included in or used in combination with drugs that may lead to an  
35 undesired level of triglycerides and/or cholesterol. Thus, a composition according to the invention may be included in or used in combination with drugs like e.g. isotretinoin and a retroviralprotease inhibitor like HIV protease inhibitors, and others.

A particulate material according to the invention has a suitable flowability as determined according to the method described in Ph.Eur. measuring the flow rate of the composition out of a funnel with a nozzle diameter of 10.0 mm. In order to avoid any adherence to the manufacturing and/or filling equipment it is important that the particulate material is freely flowing. This characteristic is also important in those cases where it is desired to process the particulate material further into other kinds of formulations such as, e.g., solid dosage forms.

As mentioned above, the particulate material according to the invention contains a vehicle. In some embodiments this vehicle has oil or oily-like character and/or is present in a relatively high amount. In such cases it may be necessary to include in the material a substance that has adsorbing or absorbing properties so that the final particulate material appears as a non-oily powder and not during storage release some of the vehicle that could result in a oily surface. Accordingly, the particulate material may contain one or more oil-sorption materials, which - when tested as described herein -

i) has an oil threshold value of 10% or more, when tested according to the Threshold Test herein, and

at least one of

ii) releases at least 30% of an oil, when tested according to the Release Test herein, and  
iii) in the form of a tablet has a disintegration time of at the most 1 hour, when tested according to Ph. Eur. Disintegration test, the tablet containing about 90% w/w or more of the oil-sorption material. In certain situations, it has been found that it is an advantage to

incorporate a sorption material in the composition in order e.g. to enable a high concentration of a vehicle has oil or oily-like character. In those cases where the vehicle has a melting point of at the most about 25°C, it may be especially suitable to incorporate a sorption material. Suitable examples of materials suitable as vehicles as well as sorption materials are given herein.

In another embodiment the invention relates to a particulate material comprising one or more fibrates and a hydrophobic or a hydrophilic or water-miscible vehicle, wherein the concentration of the vehicle is at least about 10% w/w. In the following are described vehicles suitable for use in a particulate material according to the invention.

**Hydrophobic or hydrophilic or water-miscible vehicles**

In the present context the term "a hydrophobic or a hydrophilic or water-miscible vehicle" is used in a very broad sense including oils, waxes, semi-solid materials and materials that normally are used as solvents (such as organic solvents) or cosolvents within the pharmaceutical industry, and the term also includes therapeutically and/or prophylactically active substances that are in liquid form at ambient temperature; furthermore the term includes emulsions like e.g. microemulsions and nanoemulsions and suspensions. The hydrophobic or hydrophilic or water-miscible vehicles will normally be liquid at ambient or elevated temperature (for practical reasons the max. temperature is about 250 °C). They may be hydrophilic, lipophilic, hydrophobic and/or amphiphilic materials. In a specific embodiment, the vehicle is non-aqueous.

The hydrophobic or hydrophilic or water-miscible vehicles that are suitable for use in the present context are substances or materials, which have a melting point of at least about 0 °C and at the most about 250 °C.

In specific embodiments of the invention, the hydrophobic or hydrophilic or water-miscible vehicles have a melting point of about 5 °C or more such as, e.g., about 10 °C or more, about 15 °C or more, about 20 °C or more or about 25 °C or more. As mentioned above, it normally requires addition of an oil-sorption material if vehicles are used that have such a low melting point. However, a person skilled in the art will know when it is necessary to add such an oil-sorption material.

In further embodiments of the invention, the hydrophobic or hydrophilic or water-miscible vehicles have a melting point of at least about 25 °C such as, e.g., at least about 30 °C at least about 35 °C or at least about 40 °C. For practical reasons, the melting point may normally not be too high, thus, the oil or oily-like material normally has a melting point of at the most about 300 °C such as, e.g., at the most about 250 °C, at the most about 200 °C, at the most about 150 °C or at the most about 100 °C. If the melting point is higher a relatively high temperature may promote e.g. oxidation or other kind of degradation of an active substance in those cases where e.g. a therapeutically and/or prophylactically active substance is included.

In the present context, melting points are determined by DSC (Differential Scanning Calorimetry). The melting point is determined as the temperature at which the linear increase of the DSC curve intersects the temperature axis.



Interesting hydrophobic or hydrophilic or water-miscible vehicles are generally substances, which are used in the manufacture of pharmaceuticals as so-called melt binders or solid solvents (in the form of solid dosage form), or as co-solvents or ingredients in pharmaceuticals for topical use.

5

It may be hydrophilic, hydrophobic and/or have surface-active properties. In general hydrophilic and/or hydrophobic vehicles are suitable for use in the manufacture of a particulate material or a solid dosage form according to the invention. In a specific embodiment they may be used when the release of the active substance from the pharmaceutical composition is designed to be immediate or non-modified or modified. Hydrophobic vehicles are normally used in the manufacture of a modified release pharmaceutical composition. The above-given considerations are simplified to illustrate general principles, but there are many cases where other combinations of vehicles and other purposes are relevant and, therefore, the examples above should not in any way limit the invention.

15

Typically, a suitable hydrophilic or water-miscible vehicle is selected from the group consisting of: polyether glycols such as, e.g., polyethylene glycols, polypropylene glycols; polyoxyethylenes; polyoxypropylenes; poloxamers and mixtures thereof, or it may be selected from the group consisting of: xylitol, sorbitol, potassium sodium tartrate, sucrose tribehenate, glucose, rhamnose, lactitol, behenic acid, hydroquinon monomethyl ether, sodium acetate, ethyl fumarate, myristic acid, citric acid, Gelucire 50/13, other Gelucire types such as, e.g., Gelucire 44/14 etc., Gelucire 50/10, Gelucire 62/05, Sucro-ester 7, Sucro-ester 11, Sucro-ester 15, maltose, mannitol and mixtures thereof.

25

A suitable hydrophobic or water-miscible vehicle may be selected from the group consisting of: straight chain saturated hydrocarbons, sorbitan esters, paraffins; fats and oils such as e.g., cacao butter, beef tallow, lard, polyether glycol esters; higher fatty acid such as, e.g. stearic acid, myristic acid, palmitic acid, higher alcohols such as, e.g., cetanol, stearyl alcohol, low melting point waxes such as, e.g., glyceryl monostearate, glyceryl monooleate, hydrogenated tallow, myristyl alcohol, stearyl alcohol, substituted and/or unsubstituted monoglycerides, substituted and/or unsubstituted diglycerides, substituted and/or unsubstituted triglycerides, yellow beeswax, white beeswax, carnauba wax, castor wax, japan wax, acetylate monoglycerides; NVP polymers, PVP polymers, acrylic polymers, or a mixture thereof.

35

In an interesting embodiment, the vehicle is a polyethylene glycol having an average molecular weight in a range of from about 400 to about 35,000 such as, e.g., from about 800 to about 35,000, from about 1,000 to about 35,000 such as, e.g., polyethylene glycol 1,000, polyethylene glycol 2,000, polyethylene glycol 3,000, polyethylene glycol 4,000, 5 polyethylene glycol 5,000, polyethylene glycol 6000, polyethylene glycol 7,000, polyethylene glycol 8,000, polyethylene glycol 9,000 polyethylene glycol 10,000, polyethylene glycol 15,000, polyethylene glycol 20,000, or polyethylene glycol 35,000. In certain situations polyethylene glycol may be employed with a molecular weight from about 35,000 to about 100,000.

10

In another interesting embodiment, the vehicle is polyethylene oxide having a molecular weight of from about 2,000 to about 7,000,000 such as, e.g. from about 2,000 to about 100,000, from about 5,000 to about 75,000, from about 10,000 to about 60,000, from about 15,000 to about 50,000, from about 20,000 to about 40,000, from about 100,000 to 15 about 7,000,000 such as, e.g., from about 100,000 to about 1,000,000, from about 100,000 to about 600,000, from about 100,000 to about 400,000 or from about 100,000 to about 300,000.

In another embodiment, the vehicle is a poloxamer such as, e.g. Poloxamer 188, 20 Poloxamer 237, Poloxamer 338 or Poloxamer 407 or other block copolymers of ethylene oxide and propylene oxide such as the Pluronic® and/or Tetronic® series. Suitable block copolymers of the Pluronic® series include polymers having a molecular weight of about 3,000 or more such as, e.g. from about 4,000 to about 20,000 and/or a viscosity (Brookfield) from about 200 to about 4,000 cps such as, e.g., from about 250 to about 25 3,000 cps. Suitable examples include Pluronic® F38, P65, P68LF, P75, F77, P84, P85, F87, F88, F98, P103, P104, P105, F108, P123, F123, F127, 10R8, 17R8, 25R5, 25R8 etc. Suitable block copolymers of the Tetronic® series include polymers having a molecular weight of about 8,000 or more such as, e.g., from about 9,000 to about 35,000 and/or a viscosity (Brookfield) of from about 500 to about 45,000 cps such as, e.g., from 30 about 600 to about 40,000. The viscosities given above are determined at 60 °C for substances that are pastes at room temperature and at 77 °C for substances that are solids at room temperature.

In a specific embodiment a particulate material according to the invention comprises as 35 vehicle a mixture of a polyethylene glycol and a poloxamer in a proportion (weight) of between 1:3 and 10:1, preferably between 1:1 and 5:1, more preferably between and 3:2

4:1, especially between 2:1 and 3:1, in particular about 7:3. In particular the poloxamer is poloxamer 188.

In another embodiment, polyethylene glycol is employed as a vehicle and it has an  
5 average molecular weight of about 6000 (PEG6000).

The vehicle may also be a sorbitan ester such as, e.g., sorbitan di-isostearate, sorbitan dioleate, sorbitan monolaurate, sorbitan monoisostearate, sorbitan monooleate, sorbitan monopalmitate, sorbitan monostearate, sorbitan sesqui-isostearate, sorbitan sesquioleate,  
10 sorbitan sesquistearate, sorbitan tri-isostearate, sorbitan trioleate, sorbitan tristearate or mixtures thereof.

The vehicle may also comprise a mixture of different vehicles such as, e.g., a mixture of hydrophilic and/or hydrophobic materials.

15

Other suitable vehicles may be solvents or semi-solid excipients like, e.g. propylene glycol, polyglycolised glycerides including Gelucire 44/14, complex fatty materials of plant origin including theobroma oil, carnauba wax, vegetable oils like e.g. almond oil, coconut oil, corn oil, cottonseed oil, sesame oil, soya oil, olive oil, castor oil, palm kernels oil,  
20 peanut oil, rape oil, grape seed oil etc., hydrogenated vegetable oils such as, e.g. hydrogenated peanut oil, hydrogenated palm kernels oil, hydrogenated cottonseed oil, hydrogenated soya oil, hydrogenated castor oil, hydrogenated coconut oil; natural fatty materials of animal origin including beeswax, lanolin, fatty alcohols including cetyl, stearyl, lauric, myristic, palmitic, stearic fatty alcohols; esters including glycerol stearate, glycol  
25 stearate, ethyl oleate, isopropyl myristate; liquid interesterified semi-synthetic glycerides including Miglycol 810/812; amide or fatty acid alcolamides including stearamide ethanol, diethanolamide of fatty coconut acids, acetic acid esters of mono and di-glycerides, citric acid esters of mono and di-glycerides, lactic acid esters of mono and diglycerides, mono and di-glycerides, poly-glycerol esters of fatty acids, poly-glycerol poly-ricinoleate,  
30 propylene glycol esters of fatty acids, sorbitan monostearates, sorbitan tristearates, sodium stearyl lactylates, calcium stearyl lactylates, diacetyl tartaric acid esters of mono and di-glycerides etc.

Normally, a particulate material or a solid dosage form according to the invention has a  
35 concentration of the vehicle in the particulate material or solid dosage form of about 5% w/w or more such as, e.g., about 10% w/w or more, about 15% w/w or more, about 20% w/w or more, about 25% w/w or more, about 30% w/w or more, about 35% w/w or more,

about 40% w/w or more, about 45% w/w or more, about 50 w/w or more, about 55% w/w or more, about 60% w/w or more, about 65% w/w or more, about 70% w/w or more, about 75% w/w or more, about 80% w/w or more, about 85% w/w or more, about 90% w/w or more or about 95% w/w or more.

5

In specific embodiments the concentration of the vehicle in a particulate material or solid dosage form of the invention is in a range from about 20% to about 80% w/w such as, e.g., from about 25% to about 75% w/w.

- 10 One of the advantages is that it is possible to incorporate a relatively large amount of vehicle and still have a material that is solid. Thus, it is possible to prepare solid compositions with a relatively high load of vehicle by use of an oil sorption material as mentioned above. Within the pharmaceutical field it is an advantage to be able to incorporate a relatively large amount of a vehicle (e.g. with oil or oily-like characteristics)
- 15 in a solid composition especially in those situation where the active substance does not have suitable properties with respect to water solubility (e.g. poor water solubility), stability in aqueous medium (i.e. degradation occurs in aqueous medium), oral bioavailability (e.g. low bioavailability) etc., or in those situations where it is desired to modify the release of an active substance from a composition in order to obtain a controlled, modified, delayed,
- 20 sustained and/or pulsed delivery of the active substance.

It is within the skills of the average practitioner to select a suitable vehicle being pharmaceutical acceptable, capable of dispersing, dissolving or at least partly dissolving the active substances and having a melting point in the desired range using general

25 knowledge and routine experimentation. Suitable candidate for vehicles are described in WO 03/004001, which is herein incorporated by reference.

30

In the present context, suitable vehicle are e.g. those mentioned above as well as those disclosed in WO 03/004001.

A further advantage is that the particulate material obtained is a free-flowing powder and therefore readily processable into e.g. solid dosage forms such as tablets, capsules or sachets. Normally, the particulate material has properties that are suitable in order to manufacture tablets by direct compression without addition of large amounts of further

35 additives. A suitable test for test the flowability of the particulate material is the method described in Ph.Eur. and measuring the flow rate of the material out of a funnel with a nozzle (orifice) diameter of 10.0 mm.

**Pharmaceutically acceptable excipients**

In the present context the terms "pharmaceutically acceptable excipient" are intended to  
5 denote any material, which is inert in the sense that it substantially does not have any  
therapeutic and/or prophylactic effect *per se*. Such an excipient may be added with the  
purpose of making it possible to obtain a pharmaceutical, cosmetic and/or foodstuff  
composition, which have acceptable technical properties. A particulate material or a solid  
dosage form according to the invention may contain one or more pharmaceutically  
10 acceptable excipients.

Examples on suitable excipients for use in a composition or solid dosage form according  
to the invention include fillers, diluents, disintegrants, binders, lubricants etc. or mixture  
thereof. As the composition or solid dosage form according to the invention may be used  
15 for different purposes, the choice of excipients is normally made taken such different uses  
into considerations. Other pharmaceutically acceptable excipients for suitable use are e.g.  
acidifying agents, alkalizing agents, preservatives, antioxidants, buffering agents,  
chelating agents, coloring agents, complexing agents, emulsifying and/or solubilizing  
agents, flavors and perfumes, humectants, sweetening agents, wetting agents etc.

20

Examples on suitable fillers, diluents and/or binders include lactose (e.g. spray-dried  
lactose,  $\alpha$ -lactose,  $\beta$ -lactose, Tabletose®, various grades of Pharmatose®, Microtose® or  
Fast-Floc®), microcrystalline cellulose (various grades of Avicel®, Elcema®, Vivacel®,  
Ming Tai® or Solka-Floc®), hydroxypropylcellulose, L-hydroxypropylcellulose (low  
25 substituted), hydroxypropyl methylcellulose (HPMC) (e.g. Methocel E, F and K, Metolose  
SH of Shin-Etsu, Ltd, such as, e.g. the 4,000 cps grades of Methocel E and Metolose 60  
SH, the 4,000 cps grades of Methocel F and Metolose 65 SH, the 4,000, 15,000 and  
100,000 cps grades of Methocel K; and the 4,000, 15,000, 39,000 and 100,000 grades of  
Metolose 90 SH), methylcellulose polymers (such as, e.g., Methocel A, Methocel A4C,  
30 Methocel A15C, Methocel A4M), hydroxyethylcellulose, sodium carboxymethylcellulose,  
carboxymethylene, carboxymethylhydroxyethylcellulose and other cellulose derivatives,  
sucrose, agarose, sorbitol, mannitol, dextrans, maltodextrins, starches or modified  
starches (including potato starch, maize starch and rice starch), calcium phosphate (e.g.  
basic calcium phosphate, calcium hydrogen phosphate, dicalcium phosphate hydrate),  
35 calcium sulfate, calcium carbonate, sodium alginate, collagen etc.

Specific examples of diluents are e.g. calcium carbonate, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate, microcrystalline cellulose, powdered cellulose, dextrans, dextrin, dextrose, fructose, kaolin, lactose, mannitol, sorbitol, starch, pregelatinized starch, sucrose, sugar etc.

5

Specific examples of disintegrants are e.g. alginic acid or alginates, microcrystalline cellulose, hydroxypropyl cellulose and other cellulose derivatives, croscarmellose sodium, crospovidone, polacrillin potassium, sodium starch glycolate, starch, pregelatinized starch, carboxymethyl starch (e.g. Primogel® and Explotab®) etc.

10

Specific examples of binders are e.g. acacia, alginic acid, agar, calcium carrageenan, sodium carboxymethylcellulose, microcrystalline cellulose, dextrin, ethylcellulose, gelatin, liquid glucose, guar gum, hydroxypropyl methylcellulose, methylcellulose, pectin, PEG, povidone, pregelatinized starch etc.

15

Glidants and lubricants may also be included in the second composition. Examples include stearic acid, magnesium stearate, calcium stearate or other metallic stearate, talc, waxes and glycerides, light mineral oil, PEG, glyceryl behenate, colloidal silica, hydrogenated vegetable oils, corn starch, sodium stearyl fumarate, polyethylene glycols, alkyl sulfates, sodium benzoate, sodium acetate etc.

20

Other excipients which may be included in a composition or solid dosage form of the invention are e.g. flavoring agents, coloring agents, taste-masking agents, pH-adjusting agents, buffering agents, preservatives, stabilizing agents, anti-oxidants, wetting agents, humidity-adjusting agents, surface-active agents, suspending agents, absorption enhancing agents, agents for modified release etc.

25

Other additives in a composition or a solid dosage form according to the invention may be antioxidants like e.g. ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorous acid, monothioglycerol, potassium metabisulfite, propyl gallate, sodium formaldehyde sulfoxylate, sodium metabisulfite, sodium thiosulfate, sulfur dioxide, tocopherol, tocopherol acetate, tocopherol hemisuccinate, TPGS or other tocopherol derivatives, etc. The carrier composition may also contain e.g. stabilising agents. The concentration of an antioxidant and/or a stabilizing agent in the carrier composition is normally from about 0.1 % w/w to about 5% w/w.

30

35

A composition or solid dosage form according to the invention may also include one or more surfactants or substances having surface-active properties. It is contemplated that such substances are involved in the wetting of the slightly soluble active substance and thus, contributes to improved solubility characteristics of the active substance.

5

Examples on surfactants are given in the following.

Suitable excipients for use in a composition or a solid dosage form according to the invention are surfactants such as, e.g., hydrophobic and/or hydrophilic surfactants as those disclosed in WO 00/50007 in the name of Lipocine, Inc. Examples on suitable surfactants are

- i) polyethoxylated fatty acids such as, e.g. fatty acid mono- or diesters of polyethylene glycol or mixtures thereof such as, e.g. mono – or diesters of polyethylene glycol with lauric acid, oleic acid, stearic acid, myristic acid, ricinoleic acid, and the polyethylene glycol may be selected from PEG 4, PEG 5, PEG 6, PEG 7, PEG 8, PEG 9, PEG 10, PEG 12, PEG 15, PEG 20, PEG 25, PEG 30, PEG 32, PEG 40, PEG 45, PEG 50, PEG 55, PEG 100, PEG 200, PEG 400, PEG 600, PEG 800, PEG 1000, PEG 2000, PEG 3000, PEG 4000, PEG 5000, PEG 6000, PEG 7000, PEG 8000, PEG 9000, PEG 1000, PEG 10,000, PEG 15,000, PEG 20,000, PEG 35,000,
- ii) polyethylene glycol glycerol fatty acid esters, i.e. esters like the above-mentioned but in the form of glyceryl esters of the individual fatty acids;
- iii) glycerol, propylene glycol, ethylene glycol, PEG or sorbitol esters with e.g. vegetable oils like e.g. hydrogenated castor oil, almond oil, palm kernel oil, castor oil, apricot kernel oil, olive oil, peanut oil, hydrogenated palm kernel oil and the like,
- iv) polyglycerized fatty acids like e.g. polyglycerol stearate, polyglycerol oleate, polyglycerol ricinoleate, polyglycerol linoleate,
- v) propylene glycol fatty acid esters such as, e.g. propylene glycol monolaurate, propylene glycol ricinoleate and the like,
- vi) mono- and diglycerides like e.g. glyceryl monooleate, glyceryl dioleae, glyceryl mono- and/or dioleate, glyceryl caprylate, glyceryl caprate etc.;
- vii) sterol and sterol derivatives;
- viii) polyethylene glycol sorbitan fatty acid esters (PEG-sorbitan fatty acid esters) such as esters of PEG with the various molecular weights indicated above, and the various Tween ® series;

- ix) polyethylene glycol alkyl ethers such as, e.g. PEG oleyl ether and PEG lauryl ether;
  - x) sugar esters like e.g. sucrose monopalmitate and sucrose monolaurate;
  - xi) polyethylene glycol alkyl phenols like e.g. the Triton® X or N series;
  - 5 xii) polyoxyethylene-polyoxypropylene block copolymers such as, e.g., the Pluronic® series, the Synperonic® series, Emkalyx®, Lutrol®, Supronic® etc. The generic term for these polymers is "poloxamers" and relevant examples in the present context are Poloxamer 105, 108, 122, 123, 124, 181, 182, 183, 184, 185, 188, 212, 215, 217, 231, 234, 235, 237, 238, 282, 284, 288, 331, 333, 334, 335, 338, 401, 402, 403 and 407;
  - 10 xiii) sorbitan fatty acid esters like the Span® series or Ariacel® series such as, e.g. sorbinan monolaurate, sorbitan monopalmitate, sorbitan monooleate, sorbitan monostearate etc.;
  - xiv) lower alcohol fatty acid esters like e.g. oleate, isopropyl myristate, isopropyl palmitate etc.;
  - 15 xv) ionic surfactants including cationic, anionic and zwitterionic surfactants such as, e.g. fatty acid salts, bile salts, phospholipids, phosphoric acid esters, carboxylates, sulfates and sulfonates etc.
- 20 When a surfactant or a mixture of surfactants is present in a composition or a solid dosage form of the invention, the concentration of the surfactant(s) is normally in a range of from about 0.1 – 80% w/w such as, e.g., from about 0.1 to about 20% w/w, from about 0.1 to about 15% w/w, from about 0.5 to about 10% w/w, or alternatively, from about 0.10 to about 80% w/w such as, e.g. from about 10 to about 70% w/w, from about 20 to about 25 60% w/w or from about 30 to about 50% w/w.

In a specific aspect of the invention, the at least one of the one or more pharmaceutically acceptable excipient is selected from the group consisting of silica acid or a derivative or salt thereof including silicates, silicon dioxide and polymers thereof; magnesium

30 aluminosilicate and/or magnesium aluminometasilicate, bentonite, kaolin, magnesium trisilicate, montmorillonite and/or saponite.

### **Sorption materials**

Materials such as those mentioned in the last paragraph above may be useful as a

35 sorption material for oils or oily-like materials in pharmaceuticals, cosmetics and/or foodstuff. In a specific embodiment, the material is used as a sorption material for oils or oily-like materials in pharmaceuticals. The material that has the ability to function as a



sorption material for oils or oily-like materials is also denoted "oil sorption material". As mentioned above, a vehicle suitable for use in a particular material or in a dosage form of the present invention may have oil or oily-like character and then it may be of advantage to include an oil sorption material in the composition.

5

Furthermore, in the present context the term "sorption" is used to denote "absorption" as well as "adsorption". It should be understood that whenever one of the terms is used it is intended to cover the phenomenon absorption as well as adsorption. The terms "sorption material" and "oil sorption material" is intended to have the same meaning.

10

A sorption material suitable for use according to the present invention is a solid pharmaceutically acceptable material, which - when tested as described herein -

i) has an oil threshold value of 10% or more, when tested according to the Threshold Test herein, and

15 at least one of

ii) releases at least 30% of an oil, when tested according to the Release Test herein, and

iii) in the form of a tablet has a disintegration time of at the most 1 hour, when tested according to Ph. Eur. Disintegration test, the tablet containing about 90% w/w or more of the pharmaceutically acceptable material.

20

The material is especially useful as a sorption material for oils or oily-like materials in pharmaceuticals, cosmetics and/or foodstuff, especially in pharmaceuticals.

As it appears from the above, it is important that the oil sorption material fulfils at least two tests. One of the tests is mandatory, i.e. the Threshold Test must be met. This test gives a measure for how much oil or oily-like material the oil sorption material is able to absorb while retaining suitable flowability properties. It is important that an oil sorption material for use according to the invention (with or without oil absorbed) has a suitable flowability so that it easily can be admixed with other excipients and/or further processed into compositions without significant problems relating to e.g. adherence to the apparatus involved. The test is described in the Experimental section herein and guidance is given for how the test is carried out. The Threshold Test involves the determination of the flowability of the solid material loaded with different amounts of oil.

From above it is seen that the oil threshold value normally must exceed 10% and often the oil sorption material has an oil threshold value of at least about 15%, such as, e.g., at

least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, or at least about 45%.

5 A especially suitable material for use according to the invention, Aeroperl 300, has a very high oil threshold value of about 60%. Accordingly, materials that have an oil threshold value of at least about 50%, such as, e.g., at least about 55% or at least about 60% are used in specific embodiments of the present invention.

10 Furthermore, an oil sorption material for use according to the invention must fulfill at least one further test, namely a release test and/or a disintegration test.

15 The release test gives a measure of the ability of an oil sorption material to release the oil that is absorbed to the material when contacted with water. This ability is very important especially in those situations where an active substance is contained in the oil or oily-like material. If the oil sorption material is not capable of releasing the oil from the material then there is a major risk that the active substance will only to a minor degree be released from the material. Accordingly, it is envisaged that bioavailability problems relating to e.g. poor absorption etc. will occur in such situations.

20 The requirements for the release test are that the solid pharmaceutical acceptable material - when tested as described herein -  
ii) releases at least about 30% such as, e.g., at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 60% of an oil. As it appears from the examples herein a suitable oil sorption material like Aeroperl 300  
25 has a much higher release. Therefore, in a specific embodiment of the invention, the solid pharmaceutical acceptable material - when tested as described herein -  
ii) releases at least about 65% such as, e.g., at least about 70%, at least about 75% or at least about 80% of an oil.

30 The second of the tests at least one of which an oil sorption material for use according to the invention must fulfill is a disintegration test. The test is not performed on the solid material in particular form but on a tablet made of the solid material. A requirement with respect to disintegration is important in order to ensure that the solid material - when included in solid dosage forms - does not impart unwanted properties to the dosage form  
35 e.g. leading to unwanted properties with respect to dissolution and bioavailability of the active substance contained in the dosage form. For some of the materials suitable for use according to the invention it is possible to press tablets containing 100% w/w of the solid

material itself. If this is the case, the test is carried out on such tablets. However, it is envisaged that there may be situations where it is rather difficult to prepare tablets from the solid material alone. In such cases it is possible to add pharmaceutically acceptable excipients normally used in the preparation of compressed tablets up to a concentration of 10% w/w or less. Examples on suitable pharmaceutically acceptable excipients include fillers, diluents, binders and lubricants. However, excipients, normally classified as disintegrants, should be avoided.

Accordingly, the solid pharmaceutical acceptable material for use according to invention- when tested as described herein iii) in the form of a tablet should have a disintegration time of at the most 1 hour, when tested according to Ph. Eur. Disintegration test, the tablet containing about 90% w/w or more, such as, e.g., about 92.5% w/w or more, about 95% w/w or more, about 97.5% w/w or more or about 100% of the pharmaceutically acceptable material.

In a further embodiment, the solid pharmaceutical acceptable material - when tested as described herein iii) in the form of a tablet has a disintegration time of at the most about 50 min, such as, e.g., at the most about 40 min, at the most about 30 min, at the most about 20 min, at the most about 10 min or at the most about 5 min, when tested according to Ph. Eur. Disintegration test, the tablet containing about 90% w/w or more, such as, e.g., about 92.5% w/w or more, about 95% w/w or more, about 97.5% w/w or more or about 100% of the pharmaceutically acceptable material.

In a specific embodiment, the solid material used as a sorption material fulfils all three tests. Thus, the solid pharmaceutical acceptable material - when tested as described herein -

i) has an oil threshold value of at least about 10%, such as, e.g., at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 60%,

ii) releases at least about 30% such as, e.g., at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75% or at least about 80% of an oil, and

iii) in the form of a tablet has a disintegration time of at the most 1 hour such as at the most about 50 min, at the most about 40 min, at the most about 30 min, at the most about

20 min, at the most about 10 min or at the most about 5 min, when tested according to Ph. Eur. Disintegration test, the tablet containing about 90% w/w or more, such as, e.g., about 92.5% w/w or more, about 95% w/w or more, about 97.5% w/w or more or about 100% of the pharmaceutically acceptable material.

5

Other specific embodiments of the invention are those, wherein

the solid pharmaceutical material used as a sorption material in a composition according to the invention- when tested as described herein -

10 i) has an oil threshold value of at least about 55%;

the solid pharmaceutical material - when tested as described herein -

ii) releases at least about 75% of an oil; and/or

15 the solid pharmaceutical material - when tested as described herein -

iii) in the form of a tablet has disintegration time of at the most about 10 min, when tested according to Ph. Eur. Disintegration test, the tablet containing about 97.5% w/w of the pharmaceutically acceptable material.

20

The solid pharmaceutically acceptable material used as a sorption material in a composition according to the invention is normally a particulate material in the form of e.g. powders, particles, granules, granulates etc.

25 Such particulate material that is suitable for use as an oil sorption material has normally a bulk density of about 0.15 g/cm<sup>3</sup> or more such as, e.g., at least about 0.20 g/cm<sup>3</sup> or at least about 0.25 g/cm<sup>3</sup>.

Furthermore, the oil sorption material normally has an oil absorption value of at least  
30 about 100 g oil/100 g such as, e.g., at least about 150 g oil/100 g, at least about 200 g oil/100g, at least about 250 g oil/100 g, at least about 300 g oil/100 g or at least about 400 g oil/100 g pharmaceutically acceptable material. The oil absorption value is determined as described in the experimental section herein.

35 The present inventors have found that a common feature of some of the materials suitable for use as oil sorption material is that they have a relatively large surface area. Accordingly, pharmaceutically acceptable material for use as an oil sorption material

according to the invention may have a BET surface area of at least 5 m<sup>2</sup>/g such as, e.g., at least about 25 m<sup>2</sup>/g, at least about 50 m<sup>2</sup>/g, at least about 100 m<sup>2</sup>/g, at least about 150 m<sup>2</sup>/g, at least about 200 m<sup>2</sup>/g, at least about 250 m<sup>2</sup>/g or at least about 275 m<sup>2</sup>/g.

- 5 As mentioned above one of the characteristic features of a pharmaceutically acceptable material for use as an oil sorption material according to the invention is that it retains a good flowability even if it has been loaded with oil or an oily-like material. Thus, the flowability of the pharmaceutically acceptable material loaded with 25% w/w or more such as, e.g. 30% w/w or more, 40% w/w or more, 45% w/w or more, 50% w/w or more, 55%  
10 w/w or more, 60% w/w or more, 65% w/w or more or about 70% w/w viscoelastic will normally meet the Ph. Eur. requirements.

- Notably, the oil sorption material may comprise a silica acid or a derivative or salt thereof such as, e.g., silicon dioxide or a polymer thereof as a pharmaceutically acceptable  
15 excipient. However, dependent on the quality employed a silicon dioxide may be a lubricant or it may be an oil sorption material. Qualities fulfilling the latter function seem to be most important.

- In a specific embodiment, a composition or solid dosage form according to invention  
20 comprises a pharmaceutically acceptable excipient that is a silicon dioxide product that has properties corresponding to Aeroperl® 300 (available from Degussa, Frankfurt, Germany).

- Use of an oil sorption material in compositions or dosage forms according to the invention  
25 is very advantageous for the preparation of pharmaceutical, cosmetic, nutritional and/or food compositions, wherein the composition comprises oil or an oily-like material. One of the advantages is that it is possible to incorporate a relatively large amount of oil and oily-like material and still have a material that is solid. Thus, it is possible to prepare solid compositions with a relatively high load of oil or oily-like materials by use of an oil sorption  
30 material according to the invention. Within the pharmaceutical field it is an advantage to be able to incorporate a relatively large amount of an oil or an oily-like material in a solid composition especially in those situation where the active substance does not have suitable properties with respect to water solubility (e.g. poor water solubility), stability in aqueous medium (i.e. degradation occurs in aqueous medium), oral bioavailability (e.g.  
35 low bioavailability) etc., or in those situations where it is desired to modify the release of an active substance from a composition in order to obtain a controlled, delayed, sustained

and/or pulsed delivery of the active substance. Thus, in a specific embodiment it is used in the preparation of pharmaceutical compositions.

The oil sorption material for use in the processing into solid compositions normally  
5 absorbs about 5% w/w or more, such as, e.g., about 10% w/w or more, about 15% w/w or more, about 20% w/w or more, about 25% w/w or more, about 30% w/w or more, about 35% w/w or more, about 40% w/w or more, about 45% w/w or more, about 50 w/w or more, about 55% w/w or more, about 60% w/w or more, about 65% w/w or more, about 70% w/w or more, about 75% w/w or more, about 80% w/w or more, about 85% w/w or  
10 more, about 90% w/w or more or about 95% w/w or more of an oil or an oily material and is still a solid material.

**Method for preparation of a particulate material or a solid dosage form according to the invention**

15 In another aspect, the invention relates to a method for the preparation of a pharmaceutical composition according to the invention. In general, any suitable method within the pharmaceutical field may be employed.

Previously, the present inventors have invented a method for obtaining a particulate  
20 composition that is especially suitable for incorporation of active substances that are poorly water-soluble and where it is envisaged that bioavailability problems may occur due to the poor water solubility. The pharmaceutical compositions may be prepared by any convenient method such as, e.g. granulation, mixing, spray drying etc. A particularly useful method is the method described in WO 03/004001, which is hereby incorporated by  
25 reference. Herein is described a process for the preparation of particulate material by a controlled agglomeration method, i.e. a method, which enables a controlled growth in particle size. The method involves spraying a first composition comprising e.g. the active substance and a vehicle, which has been melted, onto a second solid carrier medium. Normally, a meltable vehicle has a melting point of at least 5 °C but lower than the melting  
30 point of the active substance. The melting point of the vehicle may be in the range of 10 °C to 150 °C, such as, e.g., in the range of 30 °C to 100°C or in the range of 40 °C to 50 °C is most preferred.

Accordingly, in another aspect, the invention relates to a method of manufacturing the  
35 particulate material or the solid oral dosage form of the invention comprising the steps of:  
i) Bringing the vehicle in liquid form, if applicable,

- ii) Maintaining the liquid vehicle at a temperature below the melting point of the fibrates and/or the statins,
- iii) Dissolving the desired amount of fibrates and statins in the vehicle,
- iv) Spraying the resulting solution onto a solid carrier having a temperature below the melting point of the vehicle,
- v) Mechanically working the resulting composition to obtain particles, i.e. a particulate material, and
- vi) Optionally subjecting the particulate material to conventional methods for preparing solid dosage forms.

10

An advantage of using the controlled agglomeration method described in WO 03/004001 is that it is possible to apply a relatively large amount of a melt to a particulate material without having an undesirable growth in particle size. Accordingly, in one embodiment of the invention, the particulate material of a pharmaceutical composition has a geometric weight mean diameter  $d_{gw}$  of  $\geq 10 \mu\text{m}$  such as, e.g.  $\geq 20 \mu\text{m}$ , from about 20 to about 2000, from about 30 to about 2000, from about 50 to about 2000, from about 60 to about 2000, from about 75 to about 2000 such as, e.g. from about 100 to about 1500  $\mu\text{m}$ , from about 100 to about 1000  $\mu\text{m}$  or from about 100 to about 700  $\mu\text{m}$ , or at the most about 400  $\mu\text{m}$  or at the most 300  $\mu\text{m}$  such as, e.g., from about 50 to about 400  $\mu\text{m}$  such as, e.g., from about 50 to about 350  $\mu\text{m}$ , from about 50 to about 300  $\mu\text{m}$ , from about 50 to about 250  $\mu\text{m}$  or from about 100 to about 300  $\mu\text{m}$ .

#### **Description of a solid dispersion and solid solution based on organic solvents**

In an important embodiment of the invention, at least parts of the fibrates and statins are present in the composition in the form of a solid dispersion including a molecular dispersion and a solid solution. Normally, 10% or more such as, e.g., 20% or more, 30% or more, 40% or more, 50% or more, 60% or more, 70% or more, 80% or more, 90% or more such as, e.g., 95% or more or about 100% w/w of either the fibrates or the statins is present in the vehicle in the form of a solid dispersion (provided that at least 80% w/w of the total amount of fibrates and statins is dissolved in the vehicle).

A solid dispersion may be obtained in different ways e.g. by employing organic solvents or by dispersing or dissolving the active substance in another suitable medium (e.g. a vehicle that is in liquid form at room temperature or at elevated temperatures).

35

Solid dispersions (solvent method) are prepared by dissolving a physical mixture of the active substance (e.g. a drug substance) and the vehicle in a common organic solvent,

followed by evaporation of the solvent. The carrier is often a hydrophilic polymer. Suitable organic solvents include pharmaceutical acceptable solvent in which the active substance is soluble such as methanol, ethanol, methylene chloride, chloroform, ethylacetate, acetone or mixtures thereof.

5

Suitable water soluble vehicles include polymers such as polyethylene glycol, poloxamers, polyoxyethylene stearates, poly-ε-caprolactone, polyvinylpyrrolidone (PVP), polyvinylpyrrolidone-polyvinylacetate copolymer PVP-PVA (Kollidon VA64), poly-methacrylic polymers (Eudragit RS, Eudragit RL, Eudragit NE, Eudragit E) and polyvinyl alcohol (PVA), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), methyl cellulose, and poly(ethylene oxide) (PEO).

Polymers containing acidic functional groups may be suitable for solid dispersions, which release the active substance in a preferred pH range providing acceptable absorption in the intestines. Such polymers may be one or more selected from the group comprising hydroxypropyl methylcellulose phthalate (HMPCP), polyvinyl acetate phthalate (PVAP), hydroxypropylmethylcellulose acetate succinate (HPMCAS), alginate, carbomer, carboxymethylcellulose, methacrylic acid copolymer (Eudragit L, Eudragit S), shellac, cellulose acetate phthalate (CAP), starch glycolate, polacrylin, methyl cellulose acetate phthalate, hydroxypropylcellulose acetate phthalate, cellulose acetate terephthalate, cellulose acetate isophthalate and cellulose acetate trimellitate.

In relations to amounts of the active substances and the vehicle in the solid dispersion, the weight ratio of active substances to polymer may be in a range of from about 3:1 to about 1:20. However, narrower range of from about 3:1 to about 1:5, such as, e.g., from about 1:1 to about 1:3 or about may also be used.

The solid dispersion is preferably formed by spray drying techniques, controlled agglomeration, freeze-drying or coating on carrier particles or any other solvent removal process. The dried product contains the active substance present in the form of a solid dispersion including a molecular dispersion and a solid solution.

The pharmaceutical compositions comprising the active substance at least partly in form of a solid dispersion or solution may in principle be prepared using any suitable procedure for preparing pharmaceutical compositions known within the art.

Apart from using the organic solvent based method, solid dispersion or solid solutions of



one or more fibrates may be obtained by dispersing and/or dissolving the active compound in the carrier composition used in the controlled agglomeration method. Stabilizing agents etc. may be added in order to ensure the stability of the solid dispersion/solution.

5

### **Solid dosage forms**

A pharmaceutical composition according to the invention is in particulate form and may be employed as such. However, in many cases it is more convenient to present the composition in the form of granules, pellets, microspheres, nanoparticles and the like or in the form of solid dosage forms including tablets, capsules and sachets and the like.

A solid dosage form according to the invention may be a single unit dosage form or it may in the form of a polydepot dosage form contain a multiplicity of individual units such as, e.g., pellets, beads and/or granules.

15 Normally, a pharmaceutical composition or a solid dosage form of the invention is intended for administration via the oral, buccal or sublingual administration route.

The invention also relates to the above-mentioned presentation form. Within the scope of the invention are compositions/solid dosage forms that are intended to release the active substance in a fast release, a delayed release or modified release manner.

A solid dosage form according to the present invention comprises a pharmaceutical composition in particulate form as described above. Normally, the concentration of the pharmaceutical composition in particulate form is in a range of from about 5 to 100% w/w such as, e.g., from about 10% to about 90% w/w, from about 15% to about 85% w/w, from about 20% to about 80% w/w, from about 25% to about 80% w/w, from about 30% to about 80% w/w, from about 35% to about 80% w/w, from about 40% to about 75% w/w, from about 45% to about 75% w/w or from about 50% to about 70% w/w of the dosage form. In an embodiment of the invention, the concentration of the pharmaceutical composition in particulate form is 50% w/w or more of the dosage form.

A solid dosage form according to the invention is obtained by processing the particulate material according to the invention by means of techniques well-known to a person skilled in the art. Normally, it involves further addition of one or more of the pharmaceutically acceptable excipients mentioned herein.

The composition or solid dosage form according to the invention may also be coated with a film coating, an enteric coating, a modified release coating, a protective coating, an anti-adhesive coating etc.

- 5 A solid dosage form according to the invention may also be coated in order to obtain suitable properties e.g. with respect to release of the active substance. The coating may be applied on single unit dosage forms (e.g. tablets, capsules) or it may be applied on a polydepot dosage form or on its individual units.
- 10 Suitable coating materials are e.g. methylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, acrylic polymers, ethylcellulose, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinylalcohol, sodium carboxymethylcellulose, cellulose acetate, cellulose acetate phthalate, gelatin, methacrylic acid copolymer, polyethylene glycol, shellac, sucrose, titanium dioxide,
- 15 carnauba wax, microcrystalline wax, zein.

Plasticizers and other ingredients may be added in the coating material. The same or different active substance may also be added in the coating material.

- 20 The particulate material or solid dosage form according to the invention may be designed to release the fibrate and the statin in any suitable manner. In specific embodiments, the compositions (i.e. particulate material or the solid dosage form) may increase the bioavailability of the fibrate and/or the statin after oral administration. The active substances may be released relatively fast in order to obtain an enhanced on-set of
- 25 action, it may be released so as to follow zero or first order kinetics or it may be released in a controlled or modified manner in order to obtain a predetermined pattern of release. Plain formulations are also within the scope of the present invention.

- In a specific embodiment a solid dosage form of the invention results in an increased
- 30 bioavailability of fibrate and/or statin relative to existing commercial fibrate and/or statin dosage forms when administered to a mammal in need thereof.

- With respect to fenofibrate a solid dosage form according to the invention may provide an AUC value relative to that of commercially available Tricor<sup>®</sup> tablets of at least about 1.1, or
- 35 at least about 1.2, or at least about 1.3, or at least about 1.4, or at least about 1.5, or at least about 1.75 or more, or at least about 2.0, or at least about 2.5, or at least about 3.0, the AUC values being determined under similar conditions. Moreover, a solid dosage form

may provide a  $c_{\max}$  value relative to that of commercially available Tricor® tablets of at least about 1.1, or at least about 1.2, or at least about 1.3, or at least about 1.4, or at least about 1.5, or at least about 1.6 or more, or at least about 2.0, or at least about 2.5, or at least about 3.0, the  $c_{\max}$  values being determined under similar conditions.

5

#### Other aspects of the invention

In one embodiment, the invention relates to a pharmaceutical composition in particulate form comprising a fibrate and a statin, wherein the composition upon oral administration to a mammal in need thereof exhibits an  $AUC/AUC_{\text{Control}}$  value of at least about 1.0, the

- 10  $AUC_{\text{Control}}$  being determined using a commercially available product containing the same fibrate and/or statin, and the AUC values being determined under similar conditions.

No absolute bioavailability data based on an injectable composition is available e.g. for fenofibrate (most likely due to solubility problems in aqueous media). The commercially

- 15 available compositions containing fenofibrate include surface-active agents and/or e.g. a lipophilic medium. The surface-active agents may impart improved bioavailability and therefore, the bioavailability of such a composition may be sufficient already. However, there is still a need for developing a flexible formulation technique that enables preparation of a variety of dosage forms. Accordingly, the requirement to such improved  
20 and/or more flexible compositions may be to obtain the same or better bioavailability than already seen from the commercially available products.

Accordingly, in further embodiments the  $AUC/AUC_{\text{Control}}$  value is at least about 1.1 such as, e.g., at least about 1.2, at least about 1.3, at least about 1.4, at least about 1.5, about  
25 1.75 or more, about 1.8 or more, about 1.9 or more, about 2.0 or more, about 2.5 or more, about 2.75 or more, about 3.0 or more, about 3.25 or more, about 3.5 or more, about 3.75 or more, about 4.0 or more, about 4.25 or more, about 4.5 or more, about 4.75 or more or about 5.0 or more, the AUC values being determined under similar conditions.

- 30 In the comparison tests mentioned above, the commercially available product is Tricor® in the form of tablets or Tricor® in the form of capsules when the fibrate is fenofibrate. When the fibrate is gemfibrozil then a suitable commercially available product is Lopid®; when the fibrate is bezafibrate a suitable commercially available product is Bezalip®; when the fibrate is clofibrate then a suitable commercially available product is Atromid®; and when  
35 the fibrate is ciprofibrate then a suitable commercially available product is Lipanon®. The recommended dosage of Tricor® is 54-160 mg/day taken with food. Tricor® tablets are provided in strengths of 54 and 160 mg, whereas Tricor® capsules are provided in

strengths of 67 and 200 mg. The tablets have a higher bioavailability than the capsules. Other trade names are Lipanthyl®, Lipantil® or Catalip®.

Control compositions with respect to individual statins are mentioned above under the  
5 discussion of individual statins.

Another object of the invention is to reduce or eliminate the food effect. Thus, in another aspect, the invention relates to a pharmaceutical composition (particulate material or solid dosage form) comprising a fibrate and a statin, wherein the composition upon oral  
10 administration to a mammal in need thereof does not exhibit a significant adverse food effect as evidenced by a value of ( $AUC_{fed}/AUC_{fasted}$ ) of at least about 0.85 with a lower 90% confidence limit of at least 0.75, the AUC being determined with respect to either the fibrate or the statin or both.

15 In a specific embodiment, the pharmaceutical composition of the invention has a value of ( $AUC_{fed}/AUC_{fasted}$ ) that is about 0.9 or more such as, e.g., about 0.95 or more, about 0.97 or more or about 1 or more.

In other words, the difference between a bioequivalence parameter measured after oral  
20 administration to a mammal with and without food, respectively, is less than 25% such as, e.g., less than 20%, less than 15%, less than 10% or less than 5%.

In another aspect, the invention relates to a pharmaceutical composition in particulate form comprising a fibrate and a statin, wherein the composition upon oral administration to  
25 a mammal in need thereof is essentially bioequivalent with a commercially available product containing the same fibrate and/or the same statin when administered in the same or lower dose as the commercially available product containing the same fibrate or the same statin.

30 In specific embodiments thereof, the dose is at the most about 98% w/w such as, e.g., at the most about 95% w/w, at the most about 90% w/w, at the most about 85% w/w, at the most about 80% w/w, at the most about 75% w/w, at the most about 70% w/w, at the most about 65% w/w, at the most about 60% w/w, at the most about 55% w/w or at the most about 50% w/w of the dose of the fibrate administered in the form of a commercially  
35 available product containing the same fibrate, and/or of the dose of the statin administered in the form of a commercially available product containing the same statin.

Normally, the bioequivalence is determined by means of at least one of the following parameters:  $t_{\max}$  (time to reach maximal plasma concentration),  $c_{\max}$  (maximal plasma concentration),  $AUC_{0-t}$  (area under the curve from time 0 to time t),  $AUC_{0-\infty}$  (area under the curve from time 0 to time infinity),  $W_{50}$  (time period where the plasma concentration is 50% or more of  $c_{\max}$ ),  $W_{75}$  (time period where the plasma concentration is 75% or more of  $c_{\max}$ ) and/or MRT (mean residence time).

A major problem with treatment with a fibrate is the large intra- or inter-individual variation. Thus, in a further aspect the invention relates to a pharmaceutical composition in particulate form comprising a fibrate and a statin, wherein the composition upon oral administration to a mammal in need thereof reduces inter- and/or intra-individual variations compared to those of a commercially available product containing the same fibrate under the same conditions and in a dose that provides an equivalent therapeutic effect.

A convenient method for determining whether a suitable amount of a fibrate and/or a statin has been absorbed may be to determine the content of unchanged fibrate excreted via the feces. Thus, in one embodiment the invention relates to a solid pharmaceutical composition, wherein at most about 25% w/w such as, e.g., at the most about 20% w/w, at the most about 15% w/w, at the most about 10% w/w, at the most about 5% w/w of the fibrate and/or the statin contained in the composition is excreted in the feces after oral administration.

A pharmaceutical composition or a solid dosage form according to the invention is designed to release the fibrate in a suitable manner. Specific release patterns as well as specific absorption patterns are mentioned below.

In specific embodiments, the fibrate and/or the statin is released from the composition within about 2 hours such as, e.g., within about 1.5 hours or within about 1 hour after oral administration, and/or about 50% w/w or more of the fibrate and/or the statin is released from the composition within about 30 min after oral administration, and/or about 50% w/w or more of the fibrate and/or the statin is released from the composition within about 20 min after oral administration, and/or about 60% w/w or more of the fibrate is released from the composition within about 1.5 hours after oral administration, and/or about 60% w/w or more of the fibrate and/or the statin is released from the composition within about 1 hour after oral administration, and/or

about 70% w/w or more of the fibrate and/or the statin is released from the composition within about 1.5 hours after oral administration, and/or

about 70% w/w or more of the fibrate and/or the statin is released from the composition within about 1 hour after oral administration, and/or

- 5 about 85% w/w or more of the fibrate and/or the statin is released from the composition within about 45 min when tested in an *in vitro* dissolution test according to USP dissolution test (paddle) employing water as dissolution medium, 100 rpm and a temperature of about 37 °C.

- 10 In another embodiment about 50% w/w or more of the fibrate and/or the statin is released from the composition within about 20 min, 15 min or 10min, and/or

about 60% w/w or more of the fibrate and/or the statin is released from the composition within about 20 min or 15 min, and/or

about 70% w/w or more of the fibrate and/or the statin is released from the composition

- 15 within about 20 min or 15 min, when tested in an *in vitro* dissolution test according to USP dissolution test (paddle) employing water as dissolution medium, 100 rpm and a temperature of about 37 °C.

In a still further embodiment about 50% w/w or more of the fibrate and/or the statin

- 20 contained in the composition is absorbed within about 8 hours, 7 hours, 6 hours or 5 hours, and/or

about 60% w/w or more of the fibrate and/or statin contained in the composition is absorbed within about 8 hours or 7 hours after oral administration, and/or

about 60% w/w or more of the fibrate contained in the composition is absorbed within

- 25 about 7 hours after oral administration, and/or

about 70% w/w or more of the fibrate contained in the composition is absorbed within about 8 hours or 7 hours after oral administration.

The details and particulars disclosed under this main aspect of the invention apply *mutatis*

- 30 *mutandis* to the other aspects of the invention. Accordingly, the properties with respect to increase in bioavailability, changes in bioavailability parameters, reduction in adverse food effect as well as release of one or more fibrates etc. described and/or claimed herein for pharmaceutical compositions in particulate form are analogues for a solid dosage form according to the present invention.

35

*Materials and methods*

*Materials*

- Fenofibrate (supplied by Sigma)  
Lactose monohydrate 200 mesh (from DMV)  
Granulated silicium oxide, Aeroperl® 300, (Degussa)  
Polyethylene glycol 6000, Pluracol® E6000 (from BASF)
- 5 Poloxamer 188, Pluronic® F-68 (from BASF)  
Glyceryl monostearate, Rylo® MD50, (from Danisco Cultor), Ph.Eur.  
Avicel PH200 (microcrystalline cellulose) (from FMC)  
Magnesium stearate
- 10 Tablets, capsules or granules might be enteric coated with different types of polymers such as hydroxypropylmethylcellulose acetate succinate (Acoat), cellulose acetate phthalate CAP, hydroxypropylmethylcellulose phtalate HPMCP or methacrylic acid copolymers such as Eudragit L30D, Eudragit 100/S, Eudragit 100/L.
- 15 *Tricor tablet formulation*  
TRICOR® tablets are fenofibrate-containing tablets available for oral administration, either containing 54 mg or 160 mg of fenofibrate per tablet.

- The tablets contain the following inactive ingredients: colloidal silicon dioxide,
- 20 crospovidone, lactose monohydrate, lecithin, microcrystalline cellulose, polyvinyl alcohol, povidone, sodium lauryl sulfate, sodium stearyl fumarate, talc, titanium dioxide, xanthan gum, colorant.

#### *Equipment*

- 25 Laboratory scale fluid bed equipment: Strea-1.  
The melt feed unit is a prototype composed of separate units for heating of air supplies for the atomizer, pressure tank and feeding tube. Granulate was sieved manually and mixed with extragranular excipients in a Turbula mixer.
- 30 Tablet compression was performed on a single punch presss, Diaf TM20

#### *Methods*

- According to the method of the invention, the fenofibrate drug was dissolved into the melted vehicle(s) and applied on the particulate carrier(s) as follows:
- 35 The vehicle(s) was melted in a beaker placed in a microwave oven. The beaker was transferred to a temperature controlled heating plate supplied with magnetic stirring. Fenofibrate was dissolved slowly in the melt at a temperature of 75 °C under magnetic

stirring. The hot solution was transferred to the pressure tank for melt spray application onto the carrier in the fluid bed. The granulate product was discharged from the fluid bed and sieved through sieve 0.7 mm or 1.0 mm manually. The sieved product was blended with magnesium stearate for 0.5 min in a Turbula mixer. If an extragranular phase has to be incorporated, the extragranular phase was premixed with the granulate in 3 minutes in a Turbula mixer.

The tablet compression was performed on a single punch machine Diaf TM20.

#### 10 Threshold Test

The test involves determination of flowability according to the method described in Ph.Eur. by measuring the flow rate of the material out of a funnel with a nozzle diameter of 10.0 mm.

15 Viscoleo (medium chain triglycerides MCT; Miglyol 812 N from Condea) was added to 100 g of the solid pharmaceutically acceptable material to be tested for use according to the invention and mixed manually. The mixture obtained was sieved through sieve 0.3 mm to assure a homogenous mixture. The oil was added successively until a flow of 100 g of the mixture could not flow through the nozzle. If the material to be tested has a high bulk  
20 volume (e.g. like that of Aeroperl 300) only 50 g of the mixture is used when testing these blends. The maximal concentration of oil where flow of material could be obtained is called the Threshold Value (given as % w/w).

#### Release Test

25 A fat-soluble colorant Sudan II (BDH Gur®) obtained from BDH VWR International 14.3 mg was dissolved in 50.0 g viscoleo (fractionated medium chain triglycerides).

10 g of the oil was added to 10.0 g of the solid pharmaceutically acceptable material to be tested for use according to the present invention and mixed until the oil was fully absorbed  
30 in the solid material. The mixture was subsequently sieved through sieve 0.3 mm to achieve a homogeneous mixture.

1.00 g of the mixture was transferred to a centrifugal tube and 3.00 ml of water was added. The suspension was mixed in a blood sample turner for 1 hour and subsequently  
35 centrifuged for 10 minutes at 5000 rpm. The upper phase of oil and water was transferred carefully to a beaker and the water was evaporated in an oven at 80 °C until constant



weight. The amount of oil released from the solid material was calculated on basis of the weight of the remaining after evaporation of the water phase.

#### Disintegration Test

- 5 The disintegration time was determined according to the method described in to Ph. Eur.

#### Dissolution Test

The test was performed in accordance with Ph. Eur 2.9.3 using the paddle apparatus. The quantification was performed using HPLC with UV-detection.

- 10 Medium: 900 ml water with 0.75 % sodium lauryl sulfate (SLS)  
Rotation speed: 50 rpm  
Temperature: 37°C  
Sampling time: 10, 20, 30, 45 and 60 minutes  
Acceptance criteria: > 75 % at 45 minutes (for the stability study)

15

#### Determination of Bulk Density

The bulk density was measured by pouring 100 g of the powder in question in a 250 ml graduated cylinder. The bulk density is given as the tapped bulk density in g/ml. The determination was performed according to Ph. Eur. (apparent volume).

20

#### Determination of Oil Absorption Value

The oil absorption value is determined by adding well-defined amounts (a 10 g) of viscoleo to a well-defined amount of the pharmaceutically acceptable material (100 g) to be tested. The oil absorption value (expressed as g viscoleo/100 g material) is reached  
25 when a further addition of 10 g oil results in a material that does not have suitable properties with respect to flowability, i.e. the material does not meet the requirements when tested according to Ph.Eur. (flowability test; see above under Threshold Test herein).

#### Determination of BET Surface Area

The apparatus applied was a Micromeritics Gemini 2375. The method applied was according to USP volumetric methods based on multiple point determination.

#### Determination of Flowability

- 35 The flowability was determined according to the method described in Ph.Eur. measuring the flow rate of the material out of a funnel with a nozzle diameter of 10.0 mm.

Determination of weight variation

The tablets prepared in the Examples herein were subject to a test for weight variation performed in accordance with Ph. Eur.

5 Determination of average tablet hardness

The tablets prepared in the Examples herein were subject to a test for tablet hardness employing Schleuniger Model 6D apparatus and performed in accordance with the general instructions for the apparatus.

10 Determination of solid solution

According to the present invention, the fibrate is dissolved in a vehicle. In order to substantiate this, a test involving differential scanning calorimetry is performed. The test is performed on the particulate composition, solid dosage form or mixture of vehicle and fibrate (after the solid solution is supposed to form). Standard DSC equipment connected

15 to a PC is used.

Sample size: 10 mg in alu pans

Heating rate: 5°C /min from 27°C to 110°C

Evaluation: The fibrate and statin are considered to be in dissolved state or non-crystalline if neither fibrate nor statin endotherm peaks are observed and if the melting

20 intervals do not significantly shift compared with the vehicle alone.

Determination of geometric weight mean diameter  $d_{gw}$ 

The geometric weight mean diameter was determined by employment of a method of laser diffraction dispersing the particulate material obtained (or the starting material) in air.

25 The measurements were performed at 1 bar dispersive pressure in Sympatec Helos equipment, which records the distribution of the equivalent spherical diameter. This distribution is fitted to a log normal volume-size distribution.

When used herein, "geometric weight mean diameter" means the mean diameter of the

30 log normal volume-size distribution.

In vivo studies in Beagle dogs

In vivo studies with the purpose of determining the bioavailability of the compositions of the present invention relative to the bioavailability of the commercially available fenofibrate

35 tablet formulation, i.e. Tricor<sup>®</sup>, was performed using Beagle dogs.

The experimental work was performed in Denmark using four male Beagle dogs each having a body weight of 12-18 kg (starting weight). The studies were conducted as open, non-randomised, cross-over studies. Each animal was its own control. Oral doses of fenofibrate was administered according to the data below.

5

The dogs were fasted overnight prior to dosing (water ad libitum) and were fed 5 hours after dosing (water ad libitum). Each dog was dosed with the specified dose of fenofibrate without taking the weight of the dog into consideration.

10 Blood samples were collected at vena jugularis externa at the following points of time: Pre-dose, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours after dosing. 4 ml of blood were collected, mixed with EDTA, and the samples were frozen (-80°C). The blood samples were analyzed using on-line extraction LC/MS and results were given in mg/mL.

15 The determined full blood concentration profiles of fenofibrate were treated using the Pharmacokinetic software WinNonlin ®, (Pharsight, California;USA) to calculate the pharmacokinetic parameters. All data are dose adjusted, when necessary.

The following examples serve the purpose of illustration of the invention and are not  
20 intended to limiting the scope of the present invention.

### Example 1

#### Immediate release tablet containing a fenofibrate and atorvastatin

Substance	Ingredient	%	mg
Drug	Fenofibrate	23.9	160.00
Drug	Atorvastatin	3.0	20.00
Carrier	Lactose	36.1	240.64
Vehicle	PEG 6000	25.6	170.88
Vehicle	Poloxamer 188	11.0	73.24
Excipient	Magnesium stearate	0.4	2.69
	Total	100.00	667.45

25

Fenofibrate and Atorvastatin are mainly dissolved in Polyethylene glycol 6000 and Poloxamer 188 (70:30 w/w ratio) at 70 °C. The dispersion is sprayed on 250 g lactose in a fluid bed Phast FB-100 with a Phast FS-1.7 melt-spray unit. The particular material

obtained is sieved through sieve 0.7 mm and blended with magnesium stearate for 0.5 min in a Turbula mixer.

- The powder mixture is compressed into 13 mm tablets with strength of 160 mg fenofibrate and 20 mg atorvastatin in to a 667 mg tablet with compound cup shaped.
- Mean disintegration time: 20 min, Hardness: 45 N

### Example 2

#### Immediate release tablet containing fenofibrate and pravastatin

Substance	Ingredient	%	mg
Drug	Fenofibrate	23.2	160.00
Drug	Pravastatin	5.8	40.00
Carrier	Lactose	35.0	241.00
Vehicle	PEG 6000	24.9	171.00
Vehicle	Poloxamer 188	10.6	73.00
Excipient	Magnesium stearate	0.5	3.00
	Total	100.00	688.00

10

- Fenofibrate and Pravastatin are mainly dissolved in Polyethylene glycol 6000 and Poloxamer 188 (70:30 w/w ratio) at 70 °C. The dispersion is sprayed on 250 g lactose in a fluid bed Phast FB-100 with a Phast FS-1.7 melt-spray unit. The particular material obtained is sieved through sieve 0.7 mm and blended with magnesium stearate for 0.5 min in a Turbula mixer.

15

The powder mixture is compressed into 13 mm tablets with strength of 160 mg fenofibrate and 40 mg atorvastatin into a 688 mg tablet with compound cup shaped.

Mean disintegration time: 25 min, Hardness: 47 N

20

### Example 3

#### Immediate release tablet containing fenofibrate and rosuvastatin

Substance	Ingredient	%	mg
Drug	Fenofibrate	24.3	160.00
Drug	Rosuvastatin	1.5	10.00
Carrier	Lactose	36.7	241.00
Vehicle	PEG 6000	26.0	171.00

<b>Vehicle</b>	Poloxamer 188	11.0	73.00
<b>Excipient</b>	Magnesium stearate	0.5	3.00
	<b>Total</b>	100.00	658.00

Fenofibrate and Rosuvastatin are mainly dissolved in Polyethylene glycol 6000 and Poloxamer 188 (70:30 w/w ratio) at 70 °C. The dispersion is sprayed on 250 g lactose in a fluid bed Phast FB-100 with a Phast FS-1.7 melt-spray unit. The particulate material  
 5 obtained is sieved through sieve 0.7 mm and blended with magnesium stearate for 0.5 min in a Turbula mixer.

The powder mixture is compressed into 12 mm tablets with strength of 160 mg fenofibrate and 40 mg Rosuvastatin into a 658 mg tablet with compound cup shaped.

10 Mean disintegration time: 22 min, Hardness: 41 N

#### Example 4

##### Immediate release tablet containing fenofibrate and simvastatin

<b>Substance</b>	<b>Ingredient</b>	<b>%</b>	<b>mg</b>
<b>Drug</b>	Fenofibrate	23.2	160.00
<b>Drug</b>	Simvastatin	5.8	40.00
<b>Carrier</b>	Lactose	35.0	241.00
<b>Vehicle</b>	PEG 6000	24.9	171.00
<b>Vehicle</b>	Poloxamer 188	10.6	73.00
<b>Excipient</b>	Magnesium stearate	0.5	3.00
	<b>Total</b>	100.00	688.00

15

Fenofibrate and simvastatin are mainly dissolved in Polyethylene glycol 6000 and Poloxamer 188 (70:30 w/w ratio) at 70 °C. The dispersion is sprayed on 250 g lactose in a fluid bed Phast FB-100 with a Phast FS-1.7 melt-spray unit. The particulate material is  
 20 sieved through sieve 0.7 mm and blended with magnesium stearate for 0.5 min in a

Turbula mixer.

The powder mixture is compressed into 13 mm tablets with strength of 160 mg fenofibrate and 40 mg simvastatin into a 688 mg tablet with compound cup shaped.

Mean disintegration time: 25 min, Hardness: 39 N

25

**Example 5****Tablet based on lipophilic matrix of glyceryl monostearate**

<b>Substance</b>	<b>Ingredient</b>	<b>%</b>	<b>mg</b>
<b>Drug</b>	Fenofibrate	28.0	160.00
<b>Drug</b>	Rosuvastatin	1.7	10.00
<b>Carrier</b>	Lactose 200 mesh	17.5	100.00
<b>Vehicle</b>	Glycerylmonostearate	52.4	300.00
<b>Excipient</b>	Magnesium stearate	0.4	2.00
		100.0	572.00

5

Fenofibrate and Rosuvastatin are mainly dissolved in Glyceryl monostearate at 70 °C. The solution is sprayed on 200 g lactose in a fluid bed Phast FB-100 with a Phast FS-1.7 melt-spray unit. The particulate material is sieved through sieve 0.7 mm and blended with magnesium stearate for 0.5 min in a Turbula mixer.

10

The powder mixture is compressed into 11 mm tablets with 572 mg tablet with compound cup shape.

Mean disintegration time: 45 min, Hardness: 48 N

15 **Example 6****Modified release polydepot capsule based on swelling hydrocolloid matrix of hydroxypropylcellulose**

<b>Substance</b>	<b>Ingredient</b>	<b>%</b>	<b>mg</b>
<b>Drug</b>	Fenofibrate	23.5	160.00
<b>Drug</b>	Atorvastatin	2.9	20.00
<b>Carrier</b>	HPMC 2910 3 cp	22.1	150.00
<b>Carrier</b>	Lactose 200 mesh	7.4	50.00
<b>Vehicle</b>	Glyceryl monostearate	44.1	300.00
	Total	100.00	680.00

20 Fenofibrate and Atorvastatin are mainly dissolved in Glycerylmonostearate at 70 °C. The solution is sprayed on a mixture of 50 g lactose and 150 g HPMC in a fluid bed Phast FB-

100 with a Phast FS-1.7 melt-spray unit. The particulate material is sieved through sieve 0.7 mm and filled into hard gelatine capsules (680 mg)

### Example 7

#### 5 Immediate release tablet

Substance	Ingredient	%	mg
Drug	Fenofibrate	33.5	160.00
Drug	Pravastatin	8.4	40.00
Oil-sorption material	Aeroperl 300	15.7	75.00
Vehicle	PEG 3000	41.8	200.00
Excipient	Magnesium stearate	0.6	3.00
	Total	100.00	478.00

Fenofibrate and Pravastatin are mainly dissolved in Polyethylene glycol 3000 at 70 °C. The dispersion is sprayed on 250 g Aeroperl in a fluid bed Phast FB-100 with a Phast FS-1.7 melt-spray unit. The particulate material is sieved through sieve 0.7 mm and blended  
10 with magnesium stearate for 0.5 min in a Turbula mixer.

The powder mixture is compressed into 11 mm tablets with strength of 160 mg fenofibrate and 40 mg atorvastatin into a 478 mg tablet with compound cup shaped.

Mean disintegration time: 29 min, Hardness: 51 N

15

### Example 8

#### Solid dosage forms according to the invention

The following compositions were prepared according to the method described in Example 1 above.

20

Substance	Ingredient	A mg (%)	B mg (%)	C mg (%)	D mg (%)	E mg (%)
Drug	Fenofibrate	160.09	50.05	50.08	50.09	159.99
Drug	Atorvastatin	-	15.0	-	-	20.0
Drug	Rosuvastatin	10.0	-	-	-	-
Drug	Pravastatin	-	-	-	15.0	-
Drug	Simvastatin	-	-	15.0	-	-
Vehicle 1	PEG6000	208.12	171.09	124.29	-	-
	PEG4000	-	-	-	244.57	-

	GMS	-	-	-	-	86.15
<b>Vehicle 2</b>	Poloxamer188	89.19	73.33	53.27	-	-
<b>Carrier</b>	Lactose	356.51	231.87	-	232.02	163.01
	Aeroperl 300	-	-	63.89	-	-
<b>Excipients</b>	Mg stearate	4.09	2.65	1.47	5.32	8.35
	Avicel	-	-	-	-	417.50

**Example 9****Preferred ranges of fenofibrate and a statin in a composition according to the****5 invention**

Compositions e.g. as described in Examples 1-7 can be varied in order to adjust the contained amount of the fibrate and the statin. A person skilled in the art will know how to adjust the amount of active substances and the pharmaceutically acceptable excipients without departing from the inventive object. In the following is given suitable ranges for

**10 fenofibrate and individual statins in compositions of the invention**

Fenofibrate 140 – 170 mg

in combination with

either:

**15 Atorvastatin 10 – 80 mg**

Fluvastatin 20 – 80 mg

Lovastatin 20 – 80 mg

Pitavastatin 2 – 4 mg

Pravastatin 10 – 80 mg

**20 Rosuvastatin 5 – 40 mg**

Simvastatin 5 – 80 mg

**Example 10****Stability of compositions according to the invention****25 For drug substances like fenofibrate and statins moisture is a significant threat to the stability of the compounds. This is especially true when one tries to formulate two unstable compounds into on single tablet unit. Very small amounts of moisture/water can significantly increase the “drug interaction” degradation. Also crystal growth is a potential threat for moisture containing combination products.**



By the uniqueness of the formulation, the avoidance of water in the process, and the careful selection of low water containing ingredients, excellent stability of the compounds is ensured. On an average the total water content of the final formulation is below 0.5 % w/w. The polymer matrix serves as a moisture/oxygen protective cover of the labile molecules.

### Example 10

#### Formulations for *in vivo* studies in dogs

Compositions of the invention were investigated in *in vivo* studies in dog. As fenofibrate is a drug substance that has major bioavailability problems, the study was primarily to investigate whether an improved bioavailability could be obtained. Accordingly, no data with respect to the statin component is available.

Tablets of 50 mg and 160 mg strength with respect to fenofibrate, respectively and having the following compositions were prepared as described in Example 1:

Substance	Ingredient	A mg	B mg	C mg	D mg	E mg
Drug	Fenofibrate	160.09	50.05	50.08	50.09	159.99
Vehicle 1	PEG6000	208.12	171.09	124.29	-	-
	PEG4000	-	-	-	244.57	-
	GMS (Rylo)	-	-	-	-	86.15
Vehicle 2	Poloxamer188	89.19	73.33	53.27	-	-
Carrier	Lactose	356.51	231.87	-	232.02	163.01
	Aeroperl 300	-	-	63.89	-	-
Excipients	Mg stearate	4.09	2.65	1.47	5.32	8.35
	Avicel	-	-	-	-	417.50
Total		818.00	529.00	293.00	532.00	835.00
Hardness	N	60	44	44	47	102
Disintegration time	Minutes	25	14	30	48	>55
Diameter	Mm	Oblong	12	12	10	Oblong

### Example 11

#### Dissolution tests

The tablet formulation A from Example 10 was subjected to a dissolution test as described in Methods with the following results:

Time (min)	% dissolved
0	0
10	28
20	56
30	74
45	88
60	97

## 5 Example 12

### Stability tests

Samples of the tablet formulation A from Example 10 was stored under the following conditions, respectively, and subjected to a dissolution (stability) test as described in Methods after 1 month and 3 months of storage; % dissolved is the percentage of

10 fenofibrate dissolved after 45 minutes:

Months	% dissolved		
	25°C and 60% RH	30°C and 65% RH	40°C and 75% RH
0	88	-	-
1	99	88	90
3	90	97	90

15 Samples of the tablet formulation A was stored under the following conditions, respectively, and subjected to a fibrate assay with the following results:

Months	mg fenofibrate		
	25°C and 60% RH	30°C and 65% RH	40°C and 75% RH
0	163.8	-	-
1	161.9	160.1	160.8
3	162.6	164.9	164.4

20 Samples of the inventive tablet formulation A was stored under the following conditions, respectively, and subjected to a degradation product test according to Ph. Eur.

(Degradation products A, B, G and Unknown accumulated into Total Degradation Product; HPLC method) with the following results:

Months	Total Degradation Product, %w/w, impurity		
	25°C and 60% RH	30°C and 65% RH	40°C and 75% RH
0	0.05	-	-
1	0.05	0.05	0.05
3	0.05	0.05	0.05

5

### Example 13

#### In vivo study in dogs

An in vivo study of formulation A from Example 10 160 mg in Beagle dogs, performed as described above under Methods, relative to Tricor<sup>®</sup>, 160 mg (Batch no.: 098212E21),

10 gave the following results:

Blood concentrations (mg/mL) (average of 4 dogs) after administration of formulation:

Time (hr)	Formulation	
	Tricor <sup>®</sup> (160mg)	Invention, A (160 mg)
0	n.a.	n.a.
0.5	367.5	995.8
1.0	612.5	2209.3
1.5	722.0	2627.8
2.0	725.8	2097.3
3.0	443.8	1219.5
4.0	295.3	930.5
6.0	160.5	642.0
8.0	250.3	869.5
12.0	211.8	615.3
24.0	133.3	394.0
48.0	n.a.	164.5

Relative bioavailability based on AUC (invention, A/Tricor<sup>®</sup>): 306%.

15 Relative  $c_{\max}$ (invention, A/Tricor<sup>®</sup>): 356%.

### Example 14

**In vivo study in dogs**

A second in vivo study of formulation A (Example 10), 160 mg in Beagle dogs, performed as described above under Methods, relative to Tricor®, 160 mg (Batch no.: 098212E21), gave the following results:

5

Blood concentrations (mg/mL) (average of 4 dogs) after administration of formulation:

Time (hr)	Formulation	
	Tricor® (160mg)	Invention, A (160 mg)
0	0	0
0.5	339.3	3616.0
1.0	1318.8	3724.8
1.5	1313.3	2982.0
2.0	1390.0	2355.8
3.0	1361.3	1359.5
4.0	1019.3	1309.5
6.0	969.3	973.8
8.0	667.0	1113.0
12.0	390.3	768.5
24.0	183.3	295.0
48.0	85.0	302.0

Relative bioavailability based on AUC (invention, A/Tricor®): 198%.

10 Relative  $c_{\max}$ (invention, A/Tricor®): 238%.

**Example 15****In vivo study in dogs**

15 An in vivo study of the formulations B, C and D (Example 10), 2x50 mg in Beagle dogs, performed as described above under Methods, relative to Lipanthyl®67M, 2x67 mg (Batch no.: 75641), gave the following results:

Blood concentrations (mg/mL) (average of 4 dogs) after administration of formulation:

Time (hr)	Formulation			
	Lipanthyl®67M (2x67mg)	Invention, B (2x50 mg)	Invention, C (2x50 mg)	Invention, D (2x50 mg)
0	0	0	0	0

0.5	187.3	2769.5	227.3	546.0
1.0	669.5	3526.8	521.5	1381.5
1.5	960.3	3106.3	858.3	1615.5
2.0	895.3	2938.0	989.3	1566.8
3.0	433.0	2465.5	902.5	1503.3
4.0	240.0	1492.3	783.8	1719.0
6.0	77.8	809.5	655.8	1034.5
8.0	79.3	1202.8	409.0	1056.0
12.0	291.3	848.0	269.8	597.3
24.0	82.5	378.0	163.8	282.8
48.0	19.3	18.8	51.5	36.5
72.0	0	0	0	0

Relative bioavailability based on AUC (invention, B/ Lipanthyl®67M): 532%.

Relative  $c_{\max}$ (invention, BA/Lipanthyl®67M): 548%.

Relative bioavailability based on AUC (invention, C/ Lipanthyl®67M): 228%.

5 Relative  $c_{\max}$ (invention, C/Lipanthyl®67M): 161%.

Relative bioavailability based on AUC (invention, D/ Lipanthyl®67M): 424%.

Relative  $c_{\max}$ (invention, D/Lipanthyl®67M): 329%.

**Claims**

1. A particulate material comprising as active substances one or more fibrates and one or more statins or a pharmaceutically active salt thereof, wherein at least 80% w/w of the total amount of active substances is dissolved in vehicle selected from the group consisting of a hydrophobic, a hydrophilic and a water-miscible vehicles.
2. A particulate material according to claim 1, wherein at least 85% w/w, at least 90% w/w, at least 95% w/w, at least 98% w/w, at least 99% w/w or at least 99.9% w/w of the total amount of active substances is dissolved in the vehicle.
3. A particulate material according to claim 1 or 2 having a suitable flowability as determined according to the method described in Ph.Eur. measuring the flow rate of the composition out of a funnel with a nozzle diameter of 10.0 mm.
4. A particulate material according to any of the preceding claims further comprising one or more oil-sorption materials, which - when tested as described herein -
- i) has an oil threshold value of 10% or more, when tested according to the Threshold Test herein, and
  - ii) releases at least 30% of an oil, when tested according to the Release Test herein, and
  - iii) in the form of a tablet has a disintegration time of at the most 1 hour, when tested according to Ph. Eur. Disintegration test, the tablet containing about 90% w/w or more of the oil-sorption material.
5. A particulate material according to any of the preceding claims, wherein the vehicle has a melting point of at the most about 250°C.
6. A particulate material according to claim 1, wherein the vehicle is hydrophobic.
7. A particulate material according to claim 6, wherein the hydrophobic vehicle is selected from the group consisting of straight chain saturated hydrocarbons, paraffins; fats and oils such as cacao butter, beef tallow, lard; low melting point waxes such yellow beeswax, white beeswax, carnauba wax, castor wax, japan wax, substituted and/or unsubstituted triglycerides, acrylic polymers, and mixtures thereof.
8. A particulate material according to claim 1, wherein the vehicle is hydrophilic or water-miscible.

9. A particulate material according to claim 8, wherein the hydrophilic or water-miscible vehicle is selected from the group consisting of polyethylene glycols, polyoxyethylene oxides, poloxamers, polyoxyethylene stearates, poly-epsilon caprolactone, fatty acids, monoglycerides, diglycerides, fatty alcohols, fractionated phospholipids and mixtures thereof.
10. A particulate material according to claim 8, wherein the hydrophilic or water-miscible vehicle is selected among polyglycolized glycerides such as Gelucire®.
11. A particulate material according to claim 8, wherein the hydrophilic or water-miscible vehicle is selected from the group consisting of polyvinylpyrrolidones, polyvinyl-polyvinylacetate copolymers (PVP-PVA), polyvinyl alcohol (PVA), polymethacrylic polymers (Eudragit RS; Eudragit RL, Eudragit NE, Eudragit E), cellulose derivatives including hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), methylcellulose, sodium carboxymethylcellulose, hydroxyethyl cellulose, pectins, cyclodextrins, galactomannans, alginates, carragenates, xanthan gums, NVP polymers, PVP polymers and mixtures thereof.
12. A particulate material according to claim 9, wherein the vehicle is a polyethylene glycol (PEG).
13. A particulate material according to claim 12, wherein the polyethylene glycol has an average molecular weight of at least 1500.
14. A particulate material according to claim 8 comprising a mixture of two or more hydrophilic or water-miscible vehicles.
15. A particulate material according to claim 14, wherein the mixture comprises a polyethylene glycol and a poloxamer in a proportion of between 1:3 and 10:1, preferably between 1:1 and 5:1, more preferably between 3:2 and 4:1, especially between 2:1 and 3:1, in particular about 7:3.
16. A particulate material according to claim 15, wherein the poloxamer is poloxamer 188.
17. A particulate material according to claim 15, wherein the polyethylene glycol has an average molecular weight of about 6000 (PEG6000).

18. A particulate material according to claim 1, wherein the vehicle is non-aqueous.
19. A particulate material according to any of the preceding claims, wherein the  
5 concentration of the vehicle is at least about 10% w/w.
20. A particulate material according to any of the preceding claims, wherein the  
concentration of the vehicle is about 15% w/w or more, about 20% w/w or more, about  
25% w/w or more, about 30% w/w or more, about 35% w/w or more or about 40% w/w or  
10 more.
21. A particulate material according to any of the preceding claims, wherein the one or  
more fibrates are selected from the group consisting of gemfibrozil, fenofibrate,  
bezafibrate, clofibrate, ciprofibrate and active metabolites and analogues thereof including  
15 any relevant fibric acid such as fenofibric acid.
22. A particulate material according to any of the preceding claims, wherein the fibrate is  
fenofibrate or an analogue thereof.
- 20 23. A particulate material according to any of the preceding claims, wherein the  
concentration of fibrate in the vehicle is at least 10% w/w, based on the total weight of the  
fibrate, the statin and the vehicle.
24. A particulate material according to any of the preceding claims, wherein the  
25 concentration of fibrate in the vehicle is at least 15% w/w, or at least 16% w/w, or at least  
17% w/w, or at least 20% w/w, preferably at least 25% w/w, more preferably at least 30%  
w/w, especially at least 35% w/w, based on the total weight of the fibrate, the statin and  
the vehicle.
- 30 25. A particulate material according to any of the preceding claims, wherein the one or  
more statins are selected from the group consisting of simvastatin, atorvastatin, lovastatin,  
pravastatin, rosuvastatin and fluvastatin, and pharmaceutically acceptable salts thereof.
26. A particulate material according to any of the preceding claims, wherein the  
35 concentration of statin in the vehicle is at least 1% w/w, based on the total weight of the  
fibrate, the statin and the vehicle.



27. A particulate material according to any of the preceding claims, wherein the concentration of statin in the vehicle is at least 1.5% w/w, or at least 2.5% w/w, or at least 5% w/w, or at least 7.5% w/w or at least 10% w/w, based on the total weight of the fibrate, the statin and the vehicle.
- 5
28. A particulate material according to any of the preceding claims containing fenofibrate and simvastatin or a pharmaceutically acceptable salt thereof.
29. A particulate material according to any of claims 1-27 containing fenofibrate and atorvastatin or a pharmaceutically acceptable salt thereof.
- 10
30. A particulate material according to any of claims 1-27 containing fenofibrate and lovastatin or a pharmaceutically acceptable salt thereof.
31. A particulate material according to any of claims 1-27 containing fenofibrate and pravastatin or a pharmaceutically acceptable salt thereof.
- 15
32. A particulate material according to any of claims 1-27 containing fenofibrate and rosuvastatin or a pharmaceutically acceptable salt thereof.
- 20
33. A particulate material according to any of claims 1-27 containing fenofibrate and fluvastatin or a pharmaceutically acceptable salt thereof.
34. A particulate material according to any of the preceding claims having a moisture content of at the most about 2.5% w/w water.
- 25
35. A particulate material according to any of the preceding claims having a moisture content of at the most about 2% w/w or 1% w/w water.
36. A particulate material according to any of the preceding claims having a storage stability of 2 months or more when tested at 40 °C and 75% RH.
- 30
37. A particulate material according to any of the preceding claims having a storage stability of 3 months or more, 4 months or more, 5 months or more or 6 months or more when tested at 40 °C and 75% RH.
- 35

38. A particulate material according to any of the preceding claims for use in the manufacture of beads, granules, granulates, pellets, powders, microspheres, and nanoparticles.
- 5 39. A particulate material according to any of the preceding claims for use in the manufacture of a solid dosage form.
40. A particulate material according to claim 39, wherein the solid dosage form is intended for administration via the oral, buccal or sublingual administration route.
- 10 41. A particulate material according to claim 39 or 40, wherein the solid dosage form is in the form of tablets including effervescent tablets, or in the form of capsules or sachets.
42. A particulate material according to any claims 1-40 for use in the manufacture of  
15 tablets obtained by direct compression.
43. A particulate material according to any of the preceding claims, wherein the particulate material has a geometric weight mean diameter  $d_{gw}$  of  $\geq 10 \mu m$  such as, e.g.  $\geq 20 \mu m$ , from about 20 to about 2000, from about 30 to about 2000, from about 50 to about 2000,  
20 from about 60 to about 2000, from about 75 to about 2000 such as, e.g. from about 100 to about 1500  $\mu m$ , from about 100 to about 1000  $\mu m$  or from about 100 to about 700  $\mu m$ , or at the most about 400  $\mu m$  or at the most 300  $\mu m$  such as, e.g., from about 50 to about 400  $\mu m$  such as, e.g., from about 50 to about 350  $\mu m$ , from about 50 to about 300  $\mu m$ , from about 50 to about 250  $\mu m$  or from about 100 to about 300  $\mu m$ .
- 25 44. A particulate material according to any of the preceding claims comprising one or more pharmaceutically acceptable excipient selected from the group consisting of fillers, disintegrants, binders, diluents, lubricants and glidants.
- 30 45. A particulate material according to any of the preceding claims further comprising an pharmaceutically acceptable additive selected from the group consisting of flavoring agents, coloring agents, taste-masking agents, pH-adjusting agents, buffering agents, preservatives, stabilizing agents, anti-oxidants, wetting agents, humidity-adjusting agents, surface-active agents, suspending agents, absorption enhancing agents.
- 35 46. A particulate material according to claim 44, wherein at least one of the one or more pharmaceutically acceptable excipient is selected from the group consisting of silica acid

or a derivative or salt thereof including silicates, silicon dioxide and polymers thereof; magnesium aluminosilicate and/or magnesium aluminometasilicate, bentonite, kaolin, magnesium trisilicate, montmorillonite and/or saponite.

5 47. A particulate material according to claim 46 comprising a silica acid or a derivative or salt thereof.

48. A particulate material according to claim 46 comprising silicon dioxide or a polymer thereof.

10

49. A particulate material according to claim 46 comprising Aeroperl® 300.

50. A solid dosage form comprising a particulate material as defined in any of claims 1-49.

15 51. A solid dosage form according to claim 50 having a storage stability of 2 months or more when tested at 40 °C and 75% RH.

52. A solid dosage form according to claim 50 or 51 having a storage stability of 3 months or more, 4 months or more, 5 months or more or 6 months or more when tested at 40 °C  
20 and 75% RH.

53. A dosage form according to any of claims 50-52, wherein at least 75% of the fibrate and/or the statin is released from the composition within about 45 min when tested in an *in vitro* dissolution test according to Ph. Eur. dissolution test (paddle) employing water with  
25 0.75% sodium lauryl sulfate as dissolution medium, 50 rpm and a temperature of about 37 °C.

54. A solid dosage form according to claim 53, wherein the dissolution test is carried out after 1 month of storage at a temperature of about 40°C and a relative humidity of about  
30 75%.

55. A solid dosage form according to any of claims 50-54, wherein the concentration of the particulate material is in a range of from about 5% to 100% w/w such as, e.g., from  
35 about 10% to about 90% w/w, from about 15% to about 85% w/w, from about 20% to about 80% w/w, from about 25% to about 80% w/w, from about 30% to about 80% w/w,

from about 35% to about 80% w/w, from about 40% to about 75% w/w, from about 45% to about 75% w/w or from about 50% to about 70% w/w of the dosage form.

56. A solid dosage form according to claim 55, wherein the concentration of the particulate  
5 material is 50% w/w or more of the dosage form.

57. A solid dosage form according to claim 50 comprising a multiplicity of individual units such as, e.g., pellets, beads and/or granules.

10 58. A solid dosage form according to claim 50 in the form of tablets, capsules or sachets.

59. A solid dosage form according to claim 58 in the form of a tablet.

60. A solid dosage form according to any of claims 57-59, wherein the individual units or  
15 solid dosage form are coated with a coating selected from the group consisting of film coatings, modified release coatings, enteric coatings, protective coatings and anti-adhesive coatings.

61. A solid dosage form according to claim 50, wherein the active substances are  
20 embedded in a matrix that releases the fibrate by diffusion.

62. A solid dosage form according to claim 61, wherein the matrix remains substantially intact during the period of drug release.

25 63. A solid dosage form according to claim 50, wherein the active substances are embedded in a matrix that release the fibrate by eroding.

64. A solid dosage form according to claim 50, wherein the active substances are released from the dosage form by diffusion through a substantially water-insoluble  
30 coating.

65. A solid dosage form according to claim 50 in the form of a polydepot dosage form, which - upon administration - disintegrates into a multiplicity of individual units from which the active substances are released.

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66. A solid dosage form according to any of claims 50-65 having a moisture content of at the most about 2.5% w/w water.

67. A solid dosage form according to any of claims 50-66 having a moisture content of at the most about 2% w/w or 1% w/w water.

5 68. A solid dosage form according to claim 50 in unit dosage form, wherein the unit dosage form comprises from about 140 to about 170 mg of fenofibrate and from about 10 to about 80 mg of atorvastatin or a pharmaceutically acceptable salt thereof.

69. A solid dosage form according to claim 50 in unit dosage form, wherein the unit  
10 dosage form comprises from about 50 to about 100 mg of fenofibrate and from about 5 to about 50 mg of atorvastatin or a pharmaceutically acceptable salt thereof.

70. A solid dosage form according to claim 50 in unit dosage form, wherein the unit dosage form comprises fenofibrate and atorvastatin or pharmaceutically acceptable salt  
15 thereof and the weight ratio between fenofibrate and atorvastatin or a pharmaceutically acceptable salt thereof is from about 1:1 to about 20:1.

71. A solid dosage form according to claim 50 in unit dosage form, wherein the unit dosage form comprises from about 140 to about 170 mg of fenofibrate and from about 20  
20 to about 80 mg of fluvastatin or a pharmaceutically acceptable salt thereof.

72. A solid dosage form according to claim 50 in unit dosage form, wherein the unit dosage form comprises from about 50 to about 100 mg of fenofibrate and from about 5 to about 50 mg of fluvastatin or a pharmaceutically acceptable salt thereof.

25

73. A solid dosage form according to claim 50 in unit dosage form, wherein the unit dosage form comprises fenofibrate and fluvastatin or pharmaceutically acceptable salt thereof and the weight ratio between fenofibrate and atorvastatin or a pharmaceutically acceptable salt thereof is from about 1:1 to about 20:1.

30

74. A solid dosage form according to claim 50 in unit dosage form, wherein the unit dosage form comprises from about 140 to about 170 mg of fenofibrate and from about 20 to about 80 mg of lovastatin or a pharmaceutically acceptable salt thereof.

35 75. A solid dosage form according to claim 50 in unit dosage form, wherein the unit dosage form comprises from about 50 to about 100 mg of fenofibrate and from about 5 to about 50 mg of lovastatin or a pharmaceutically acceptable salt thereof.

76. A solid dosage form according to claim 50 in unit dosage form, wherein the unit dosage form comprises fenofibrate and fluvastatin or pharmaceutically acceptable salt thereof and the weight ratio between fenofibrate and lovastatin or a pharmaceutically acceptable salt thereof is from about 1:1 to about 20:1.

77. A solid dosage form according to claim 50 in unit dosage form, wherein the unit dosage form comprises from about 140 to about 170 mg of fenofibrate and from about 10 to about 80 mg of pravastatin or a pharmaceutically acceptable salt thereof.

78. A solid dosage form according to claim 50 in unit dosage form, wherein the unit dosage form comprises from about 50 to about 100 mg of fenofibrate and from about 5 to about 50 mg of pravastatin or a pharmaceutically acceptable salt thereof.

79. A solid dosage form according to claim 50 in unit dosage form, wherein the unit dosage form comprises fenofibrate and pravastatin or pharmaceutically acceptable salt thereof and the weight ratio between fenofibrate and pravastatin or a pharmaceutically acceptable salt thereof is from about 1:1 to about 20:1.

80. A solid dosage form according to claim 50 in unit dosage form, wherein the unit dosage form comprises from about 140 to about 170 mg of fenofibrate and from about 5 to about 80 mg of simvastatin or a pharmaceutically acceptable salt thereof.

81. A solid dosage form according to claim 50 in unit dosage form, wherein the unit dosage form comprises from about 50 to about 100 mg of fenofibrate and from about 2.5 to about 50 mg of simvastatin or a pharmaceutically acceptable salt thereof.

82. A solid dosage form according to claim 50 in unit dosage form, wherein the unit dosage form comprises fenofibrate and simvastatin or pharmaceutically acceptable salt thereof and the weight ratio between fenofibrate and simvastatin or a pharmaceutically acceptable salt thereof is from about 1:1 to about 40:1.

83. A solid dosage form according to claim 50 in unit dosage form, wherein the unit dosage form comprises from about 140 to about 170 mg of fenofibrate and from about 5 to about 40 mg of rosuvastatin or a pharmaceutically acceptable salt thereof.

84. A solid dosage form according to claim 50 in unit dosage form, wherein the unit dosage form comprises from about 50 to about 100 mg of fenofibrate and from about 2.5 to about 25 mg of rosuvastatin or a pharmaceutically acceptable salt thereof.
- 5 85. A solid dosage form according to claim 50 in unit dosage form, wherein the unit dosage form comprises fenofibrate and rosuvastatin or pharmaceutically acceptable salt thereof and the weight ratio between fenofibrate and rosuvastatin or a pharmaceutically acceptable salt thereof is from about 2:1 to about 40:1.
- 10 86. A solid dosage form according to claim 50 in unit dosage form, wherein the unit dosage form comprises from about 140 to about 170 mg of fenofibrate and from about 1 to about 10 mg of pitavastatin or a pharmaceutically acceptable salt thereof.
87. A solid dosage form according to claim 50 in unit dosage form, wherein the unit  
15 dosage form comprises from about 50 to about 100 mg of fenofibrate and from about 0.5 to about 5 mg of pitavastatin or a pharmaceutically acceptable salt thereof.
88. A solid dosage form according to claim 50 in unit dosage form, wherein the unit  
20 dosage form comprises fenofibrate and pitavastatin or pharmaceutically acceptable salt thereof and the weight ratio between fenofibrate and pitavastatin or a pharmaceutically acceptable salt thereof is from about 10:1 to about 200:1.
89. A solid dosage form according to any of claims 50-88, which results in an increased  
25 bioavailability of fibrate relative to existing commercial fibrate dosage forms when administered to a mammal in need thereof.
90. The solid dosage form according to claim 89, which provides an AUC value relative to that of commercially available Tricor<sup>®</sup> tablets of at least about 1.1, or at least about 1.2, or at least about 1.3, or at least about 1.4, or at least about 1.5, or at least about 1.75 or  
30 more, or at least about 2.0, or at least about 2.5, or at least about 3.0, the AUC values being determined under similar conditions.
91. A solid dosage form according to claim 89, which provides a  $c_{max}$  value relative to that of commercially available Tricor<sup>®</sup> tablets of at least about 1.1, or at least about 1.2, or at  
35 least about 1.3, or at least about 1.4, or at least about 1.5, or at least about 1.6 or more, or at least about 2.0, or at least about 2.5, or at least about 3.0, the  $c_{max}$  values being determined under similar conditions.

92. A solid dosage form according to any of claims 50-91, wherein the fibrate and/or the statin is stable.
- 5 93. A solid dosage form according to claim 92, wherein the fibrate and/or the statin is present in an amount of at least 90%, or at least 95%, or at least 100%, relative to the amount prior to storage, when assayed after 3 months of storage at a temperature of about 40°C and a relative humidity of about 75%.
- 10 94. A method of manufacturing the solid oral dosage form of claim 50 comprising the steps of:
- i) Bringing the vehicle in liquid form, if applicable,
  - ii) Maintaining the liquid vehicle at a temperature below the melting point of the fibrate and/or the statin,
  - 15 iii) Dissolving the desired amount of fibrate and statin in the vehicle,
  - iv) Spraying the resulting solution onto a solid carrier having a temperature below the melting point of the vehicle,
  - v) Mechanically working the resulting composition to obtain particles, i.e. a particulate material, and
  - 20 vi) Optionally subjecting the particulate material to conventional methods for preparing solid dosage forms.
95. Use of a particular material as defined in any of claims 1-49 or a solid dosage form defined in any of claims 50-93 to enhance the oral bioavailability of a fibrate, especially of
- 25 fenofibrate, and/or of a statin, especially rosuvastatin, pravastatin, atorvastatin or simvastatin.